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ARCHIVES OF PATHOLOGY

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EXPERIMENTAL LESIONS OF THE BRAIN FROM CARBON MONOXIDE*

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AND
L. H. BACON, M.D.
SAN BERNARDINO, CALIF.

At about the same time, and working independently, we made experiments to ascertain the effect of carbon monoxide on the central nervous system of animals.[1] To avoid overlapping considerations of the literature, it seems best to combine the two reports.

Accidents and deaths due to inhalation of carbon monoxide date back to antiquity. Some of the clinical symptoms and pathologic changes were reported as early as the eighteenth century. In an extensive compilation of the literature, Lewin[2] claimed that Troja in 1778 first described the cherry red color of the blood in carbon monoxide poisoning and that Piorry in 1826 also called attention to this. Bernard[3] demonstrated this phenomenon in his classes at the Collége de Françe, from 1847 to 1857. Since that time a voluminous literature has accumulated on this subject, especially as regards its clinical manifestations and morbid anatomy.

Profound disturbances of the peripheral nerves and central nervous system following poisoning with charcoal fumes and illuminating gas have been known for a long time, and in many reviews and monographs[4] the early observations are mentioned. The symptoms are of such diverse conditions as amnesia, localized paralyses, hemiplegia and com-

* Submitted for publication, June 27, 1930.

* From the Norman Bridge Pathological Laboratory, Rush Medical College.

1. The experiments performed by one of us (C. B. S.) were aided by a grant (no. 109) from the Committee on Scientific Research of the American Medical Association.

2. Lewin, L.: Die Kohlenoxydvergiftung, Berlin, Julius Springer, 1920.

3. Bernard, Claude: Leçons sur les substances toxiques et médicamenteuses, Paris, 1857.

4. The following are frequently cited:

Bourdon: Thèse sur les troubles nerveux consécutifs a l'empoisonnement par CO, Paris, 1843.

Siebenhaar and Lehmann: Die Kohlenoxydvergiftung, Ihre Erkenntnis, Verhütung und Behandlung, Dresden, 1858.

Friedberg, H.: Die Vergiftung durch Kohlendunst, Berlin, 1866.

plete dementia. They may follow the poisoning immediately or may appear many days or weeks later. Such sequences of gas poisoning, however, are rare. They occur in only a few of the many who are poisoned with carbon monoxide.

The pathologic changes reported as occurring in the organs in men and animals after carbon monoxide asphyxia are innumerable. Peterson, Haines and Webster [5] summarized the appearances in the human body as follows: Bright patches in the skin, pulmonary edema and bright red froth in the air passages; the gastric and intestinal mucosa may also show small punctiform hemorrhages; occasionally a large hemorrhage in the great omentum and leptomeninges; multiple punctiform hemorrhages and softening of the cortex and lenticular nuclei, notably in the two internal segments; kidneys may show fatty degeneration and necrosis in the convoluted tubules. Furthermore, there have been reported such changes as the following: dilation of the heart, with the blood changes of progressive pernicious anemia (Koren [6]); extensive necrosis of the myocardium (Tesseraux [7]); unilateral and bilateral gangrene (Alberti,[8] McLean,[9] Briggs [10]), and multiple sclerosis. McGurn [11] and Altschul [12] reported vascular lymphocytic infiltration of the central nervous system in four women who were asphyxiated in a burning theater.

The conspicuous changes in the brain when death takes place soon after poisoning with illuminating gas, or carbon monoxide in some other form, are hyperemia, multiple small hemorrhages and the bright

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Becker, E.: Ueber Nachkrankheiten der Kohlenoxydvergiftung, speciell über einen unter dem Bilde der multiplen Sclerose des Centralnervensystems verlaufenen Fall, Deutsche med. Wchnschr. **15**:513, 1889; Zur Lehre von den nervösen Nachkrankheiten der Kohlenoxydvergiftung, Deutsche med. Wchnschr. **19**:571, 1893.

Sachs, W.: Die Kohlenoxydvergiftung, Braunschweig, 1900.

Sibelius, C.: Die psychischen Störungen nach akuter Kohlenoxydvergiftung. Monatschr. f. Psychiat. u. Neurol. **18**:39, 1905.

5. Peterson, F.; Haines, W. S., and Webster, R. W.: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1923, vol. 2, pp. 313-314.

6. Koren, A.: Tre tilfaelde af akut forløbende perniciøs anaemi inden samme husstand, Norsk mag. f. laegevidensk. **52**:550, 1891.

7. Tesseraux, H.: Ueber ausgedehnte Myokardnekrosen bei einen Fall von Leuchtgasvergiftung, Centralbl. f. allg. Path. u. path. Anat. **42**:344, 1928.

8. Alberti: Ausgedehntes Gangrän der Halsmuskulatur und Lähmung des rechten Beins nach Kohlenoxydvergiftung, Deutsche Ztschr. f. Chir. **20**:476, 1884.

9. McLean, A.: Carbon Monoxide Poisoning with Gangrene in Both Legs, J. A. M. A. **56**:1455, 1911.

10. Briggs, J. E.: Gangrene Following Carbon Monoxide Poisoning, J. A. M. A. **73**:678, 1919.

11. McGurn, W. J.: Multiple Sclerosis Due to Repeated Inhalation of Carbon Monoxide in Furnace Gas, M. Rec. **91**:149, 1914.

12. Altschul, R.: Die Einwirkung der Kohlenoxydvergiftung auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:442, 1927.

pink or scarlet color of the blood. But if the persons poisoned live for several days, bilateral regions of softening are often found in the inner segments of the lenticular nucleus, the globus pallidus. Kolisko [13] described such bilateral softening of the lenticular nuclei as a characteristic lesion of carbon monoxide asphyxia. Previous to his report, this lesion had already been described by Friedberg,[14] and Poelchen [15] reported symmetrical softening in the anterior part of the lenticular nucleus in twelve brains. Hill and one of us [16] reported on the study of thirty-two brains in which bilateral ischemic necrosis was uniformly present. In the records of the necropsies made by Dr. E. R. LeCount, who obtained these brains, petechial or punctiform hemorrhages in the brain and leptomeninges, stomach, intestines, peritoneum, pharynx, larynx and skin are mentioned. These lesions of the brain are almost always present when, as stated, death occurs several days after coma from carbon monoxide, and by many investigators have been regarded as pathognomonic for poisoning with carbon monoxide.

None of the explanations of the action of carbon monoxide has been generally accepted. The long slender arterioles supplying the lenticular nuclei impressed Kolisko [13] so deeply that he advanced the theory of ischemia to account for the symmetrical softenings. Dilation of these arterioles, a slowed blood current, edema of the brain, pressure below by the dilated, pulsating carotid arteries and absence of any other blood supply to the globus pallidus were all emphasized by Kolisko. He also believed that the right angle at which the vessels arise from the carotids is an additional factor in causing the depleted supply of blood. These views have been widely adopted to explain the bilateral symmetrical softening of the basal ganglions in carbon monoxide poisoning. The dilation of blood vessels and the atony of the musculature in the walls of the arterioles were demonstrated by Klebs [17] many years before in the first careful study of experimental carbon monoxide poisoning.

The theory proposed by Heinecke [18] that carbon monoxide acts like a ferment has not found much support. A few have suggested that

13. Kolisko, A.: Die symmetrische Encephalomalacie in den Linsenkernen nach Kohlenoxydvergiftung, Beitr. z. gerichtl. Med. **2**:1, 1914.

14. Friedberg (footnote 4, third reference).

15. Poelchen, R.: Zur Aetiologie der Gehirnerweichung nach Kohlenoxydvergiftung, nebst einigen Bemerkungen zur Hirnquetschung, Virchows Arch. f. path. Anat. **112**:26, 1888.

16. Hill, E., and Semerak, C. B.: Changes in the Brain in Gas (Carbon Monoxide) Poisoning, J. A. M. A. **71**:644, 1918.

17. Klebs, E.: Ueber die Wirkung des Kohlenoxyd auf den tierischen Organismus, Virchows Arch. f. path. Anat. **32**:450, 1865.

18. Heinecke, W.: Die Fermentintoxication und deren Beziehung zur Sublimat- und Leuchtgasvergiftung, Deutsche Arch. f. klin. Med. **42**:147, 1887.

it may produce encephalitis.[19] It has also been suggested by a number of investigators that carbon monoxide acts directly on the nerve tissues as a tissue poison.[20] Haggard,[21] in his studies on carbon monoxide asphyxia, exposed cultures of nerve tissue of the chick to a concentration of 79 per cent of the gas in vitro; as no effect could be observed on the growing nerve cells, he concluded that carbon monoxide has no specific effect on nerve tissue, but acts in the body only through the asphyxia resulting from its combination with hemoglobin.

The recent announcement by Haldane [22] that possibly carbon monoxide may act on cellular catalysts, replacing oxygen in this respect, will probably stimulate interest in this theory. Closely related to this possibility of direct action on tissues is the conception that some tissues are particularly susceptible to the action of carbon monoxide, being especially vulnerable because of physicochemical characteristics that they possess. This theory advanced by the Vogts [23] included the introduction of a new term "pathoklise" to define the predilection of the globus pallidus. But this theory, as well as the designation to which it gave rise, found few advocates; in fact, some investigators are definitely opposed to the views advanced by the Vogts. A suggestion has recently been made that some parts of the central nervous system are much more vulnerable than others to lowered oxygen tension.[24]

The action on the walls of blood vessels to which reference has been made (Klebs [17]) has always received serious consideration in attempts to explain the action of carbon monoxide on the central nervous system. The frequency in older persons of symptoms that first appear some time after the poisoning has been explained by the presence in the walls of the vessels of changes due to old age, to which are added those caused by carbon monoxide.[25] McConnell and

19. Lesser, A.: Atlas d. gerichtl. Med. **1**:144, 1884. Oppenheim, H., and Cassirer, R.: Die Encephalitis, Vienna, Alfred Hölder, 1907, p. 15. Kobert, R.: Lehrbuch der Intoxikationen, ed. 2, Stuttgart, Ferdinand Enke, 1906, vol. 2.

20. Siebenhaar and Lehmann (footnote 4, second reference). Geppert, J.: Kohlenoxydvergiftung und Erstickung, Deutsche med. Wchnschr. **18**:418, 1892.

21. Haggard, H. W.: The Growth of Neuroblast in the Presence of Carbon Monoxide, Am. J. Physiol. **56**:390, 1921.

22. Haldane, J. B. S.: Carbon Monoxide as a Tissue Poison, Biochem. J. **21**:1069, 1927.

23. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankung der striären Systems, J. f. Psychiat. u. Neurol. **25**:633, 1920. Vogt, O.: Der Begriff der Pathoklise, ibid. **31**:242, 1922.

24. Mackay, R. P.: Neurologic Changes Following Carbon Monoxide Poisoning, J. A. M. A. **94**:1733, 1930.

25. Sibelius, C.: Zur Kenntnis der Gehirnerkrankungen nach Kohlenoxydvergiftung, Ztschr. f. klin. Med. **49**:111, 1903. Ruge, H.: Kasuistischer Beitrag zur pathologischen Anatomie der symmetrischen Linsenkernerweichung bei Kohlenoxydvergiftung (12 Fälle), Arch. f. Psychiat. **64**:150, 1921.

Spiller [26] found a marked calcification in the walls of vessels supplying regions in the brain softened from carbon monoxide poisoning. The patient recovered for a time after being unconscious for ten hours, but about three weeks later returned to the hospital with bilateral motor symptoms, intense spasticity and slight erythematous eruption of the face. Feeding with a tube was necessary because of spasticity of the deglutitory muscles. The vessels with calcified walls were within the necrotic inner segment of each lenticular nucleus. Others have also commented on the calcium deposits in the arterial walls as an effect of carbon monoxide poisoning.

An excellent description of some of these lesions of the brain was made by Mott.[27] He found small hemorrhages in the white substance of the cerebrum due to stasis and thrombosis, and these he said resulted from the extremely small channels of the vessels, the weakened heart action and the anatomic characteristics of the vessels, their terminality and absence of anastomosis. Each arteriole that perforates the cortex from the leptomeninges, as well as each in the white substance directed outward, has a brush-shaped set of capillaries altogether separate from other vessels and a separate emergent vein unconnected with adjacent veins. Many writers [28] describe fatty, hyaline and other retrogressive changes in the walls of the blood vessels, for the most part the arterioles and capillaries. Such alterations, it is believed, account for the atony of the muscular coats, dilation of the channels, slowing or cessation of the current of blood and also for the thrombosis observed by many who have studied these alterations of the brain. The opinion has also been expressed that anoxemia, which after all is at the bottom of all the untoward effects of carbon monoxide as a poison, may first so

26. McConnell, J. W., and Spiller, W. G.: A Clinicopathologic Study of Carbon Monoxid Poisoning, J. A. M. A. **59**:2122, 1912.

27. Mott, F. W.: Punctiform Hemorrhages in the Brain in Gas Poisoning, Proc. Roy. Soc. Med., London **10**:73, 1916-1917; Brit. M. J. **1**:637, 1917; Carbon Monoxide and Nickel Carbonyl Poisoning: The Systematic Examination of the Cerebral Nervous System in a Case of Poisoning by Illuminating Gas, and Two Fatal Cases of Poisoning Occurring in the Carbonyl of Nickel Works, Arch. Neurol. Path. Lab., London County Asylum, Claybury, London **3**:246, 1907.

28. Klebs (footnote 17). Poelchen, R.: Gehirnerweichung nach Vergiftung mit Kohlendunst, Berl. klin. Wchnschr. **19**:396, 1882; footnote 15. Cramer, A.: Anatomischer Befund im Gehirn einer Kohlenoxydvergiftung, Centralbl. f. allg. Path. u. path. Anat. **2**:545, 1891. Herzog, G.: Zur Pathologie der Leuchtgasvergiftung mit macro- und mikroskopischen Demonstrationen, München. med. Wchnschr. **67**:558, 1920. Weimann, W.: Ueber Hirnpurpura bei akuten Vergiftungen, Deutsche Ztschr. f. d. ges. gerichtl. Med. **2**:543, 1923. Grinker, R. R.: Ueber einen Fall von Leuchtgasvergiftung mit doppelseitiger Pallidumerweichung und schwere Degeneration des tieferen Grosshirnmarklagers, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:433, 1925.

influence the vasomotor centers in the brain that dilation of the vessels precedes all the other modifications in their walls or in the circulation through them.[29]

Many attempts have been made to produce cerebral lesions in animals by exposing them to illuminating gas. Mice, guinea-pigs, rabbits and dogs have been used. With acute poisoning, hyperemia of the brain has been regularly observed,[30] and with chronic poisoning bilateral softenings in the basal ganglions. When dogs, monkeys and cats are exposed to illuminating gas,[31] disturbances in gait or vision occur in some of the animals, and degenerative changes in the globus pallidus, the white matter and the cortex have been noted by a few investigators.

In the experiments by Grünstein and Popova,[32] the inhalation by rabbits and cats of carbon monoxide in concentrations of from 1 to 4 per cent was followed by paralysis of the hind legs. Microscopically, marked degenerative changes were found in the cord and cerebellum, with, in some of the animals, lesions in the substantia nigra, nucleus ruber and the olive; in one, a focal lesion was found in the cortex of the frontal lobe.

Capillary hemorrhages were observed in the brains of dogs by Claude.[33] Chronic encephalitis manifested by perivascular infiltration was reported by Spirtow and Chardin (cited by Lewin[2]). Sibelius,[34] described acute and chronic encephalitis and also foci of ischemia or degeneration due to changes in the arteries.

EXPERIMENTS

In an effort to produce bilateral softening of the basal ganglions one of us (C. B. S.) made the following experiments: Pure carbon monoxide or illuminating gas in high percentage was given to six rabbits and three guinea-pigs by repeated intravenous, intra-arterial or

29. Ford, F. R.: An Experimental Investigation into the Effects of Asphyxia on the Brain, with Especial Reference to Asphyxia Neonatorum, Bull. Johns Hopkins Hosp. **42**:70, 1928. Hiller, F.: Ueber die krankhaften Veränderungen im Zentralnervensystem nach Kohlenoxydvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:594, 1924.

30. Photakis, B. A.: Anatomische Veränderungen des Zentralnervensystems bei Kohlenoxydvergiftungen, Vrtljschr. f. gerichtl. Med. **62**:42, 1921.

31. Meyer, A.: Experimentelle Erfahrungen über die Kohlenoxydvergiftung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:187, 1928.

32. Grünstein, Z. M., and Popova, Nina: Experimentelle Kohlenoxydvergiftung, Arch. f. Psychiat. **85**:283, 1928.

33. Claude, Henry: On Nature of Nerve Injuries Caused by Carbon Monoxide Poisoning, Tr. Internat. Cong., 1913, London, sect. 11, Neuropath., pt. 2, 1914, p. 343.

34. Sibelius (footnote 4, sixth reference; footnote 24).

intra-abdominal injections, under a glass globe. The carbon monoxide used was produced by the action of sulphuric acid on oxalic acid, the carbon dioxide being absorbed by running the gas through a solution of potassium hydroxide, then washing it in distilled water and finally drying it by means of a calcium tube. The illuminating gas used contained about 17 per cent carbon monoxide.

The amount of gas given intravenously was from 10 to 25 cc.; the amount given intraperitoneally or by inhalation was from 120 to 480 cc. Two experiments were performed weekly, making from seven to forty-two in the different animals. Necropsies were performed immediately if possible, otherwise within a few hours after death. Pieces were taken from many organs and hardened in neutral 10 per cent formaldehyde solution. Sections of the visceral organs were stained with hematoxylin and eosin. The brain, medulla, spinal cord and cerebellum were cut in various regions, and the sections were further stained with the sudan III, hematoxylin-phosphotungstic acid, Weigert-Pal, Marchi, Del Rio Hortega and Mann stains. There were no changes in the animals that received intravascular injections. The intraperitoneal injections produced slight alterations. Hyperemia of all organs and cherry red color of the blood were present in all animals gassed by inhalation. Capillary hemorrhages in the lungs with fatty infiltration of the liver was found in one rabbit and one guinea-pig; in two rabbits there was a slight perivascular lymphocytic infiltration of the brain, medulla and spinal cord. In most animals there were no clinical manifestations, except coma; in two rabbits and a guinea-pig, a fleeting paralysis of the hindlegs was noticed. The results of these experiments proved unsatisfactory. The paucity of changes thus obtained could have apparently only one explanation, that rabbits and guinea-pigs eliminate carbon monoxide before serious pathologic changes take place. Therefore other experiments, in which five rabbits, four guinea-pigs and three dogs were used, were begun.

All the animals were subjected almost daily to a weak current of illuminating gas until they were completely unconscious. The exposures lasted for from forty-five minutes to four hours. In the course of these experiments, the endeavor was made to ascertain the difference in resistance to the gas and in time of elimination of it, in the different animals.

The percentage of carbon monoxide in the blood was measured every fifteen to twenty-five minutes from the moment unconsciousness took place until carbon monoxide hemoglobin was zero. A rapid drop was noticed during the first hour, down to 40 per cent in the dogs, 25 per cent in the guinea-pigs and 20 per cent in the rabbits; during the second and especially the third hour, the gas was eliminated more

slowly (fig. 1). The weight was recorded twice a week; there was considerable loss in the dogs as compared with the rabbits and guinea-pigs.

In the fresh and hardened brains there were no visible changes grossly, except hyperemia. By microscopic examination, bilateral ischemic necrosis was found in the central nuclei in one dog, one rabbit and one guinea-pig.

The dog had been gassed for twenty-two hours from November 29 until December 21 and had lost during this period 4 pounds 2 ounces (1.85 Kg.) from the original weight, 13 pounds 12 ounces (6.2 Kg.). Microscopic examination of the brain revealed a region of marked ischemic softening involving the whole lenticular nucleus and more than one half of the thalamus. The ganglion cells in this region consisted

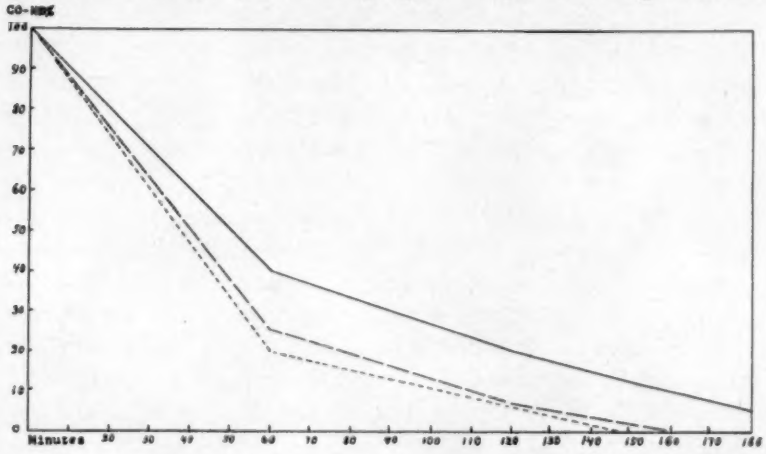

Fig. 1.—The rate of elimination of carbon monoxide from the blood of dogs, guinea-pigs and rabbits. The solid line represents the rate in dogs; the dash line, that in guinea-pigs, and the dotted line, that in rabbits.

of long, narrow, elliptic structures, very dark-staining and in various stages of karyorrhexis; at the periphery of the focus of necrosis the cells were swollen and pale; the Nissl granules had completely disappeared, and in some cells the body was a faint shadow without visible nucleus or nucleolus. Many of the Betz giant cells had suffered similar retrogressive changes. The pyramidal cells of the cortex were shrunken, their nuclei narrow and triangular, their dendrites very dark staining and visible for a long distance. Purkinje's cells varied in size and shape, their cell bodies were sharp edged, the nuclei pale and vesicular; occasionally a short, swollen, pale dendrite was seen. Similar changes were found in the cells of the anterior horns of the spinal cord. The glia cells and fibrils were not noticeably changed. In all sections of the brain, cerebellum, medulla and spinal cord there were small, perivascular

and capillary hemorrhages, from one to four per square centimeter; a few small hemorrhages were also seen in the cerebral leptomeninges. All the veins were distended with erythrocytes, the arteries in general being empty. The larger arteries in several sections of the brain stem were fenestrated and sclerosed, many calcified, the lime deposit completely replacing the vascular substance, especially in sections through the brain stem and cerebellum.

The microscopic changes in the central nervous system of the rabbit and guinea-pig, where the exposure to carbon monoxide had produced a bilateral ischemic necrosis, were similar in all respects save an absence of calcification of the arteries. The rabbit was exposed for sixty hours to carbon monoxide and lost 1 pound (0.5 Kg.) in weight during that period; the guinea-pig, gassed for eighty-two hours, lost only 1 ounce (0.05 Kg.).

Petechial or perivascular hemorrhages of the brain or leptomeninges were present in two dogs, two rabbits and four guinea-pigs; perivascular lymphocytic infiltration in two dogs and two rabbits; and sclerosis of the cerebral arteries in two dogs and one guinea-pig. More or less atrophy of the large ganglion cells was found in all animals, as well as hyperemia of the brain and leptomeninges. Except for hemorrhages in the lungs and fatty changes in the liver, the visceral changes were insignificant.

From these few experiments it appears as though changes caused by carbon monoxide differ in different animals. This may be due to individual variations of tolerance or resistance. According to Douglas, Haldane and Haldane:[35]

> When a solution of Hb, whether enclosed in blood corpuscles or free, is saturated in the presence of a gas mixture containing O_2 and CO, the ratio of oxyhemoglobin to carbon monoxide hemoglobin is always proportional to the relative partial pressure of O_2 and CO. It is not altered by the presence of CO_2 or slight changes in reaction or of reduced hemoglobin or by dilution. However, it is appreciably altered by temperature as well as by light and varies distinctly in the hemoglobin of different individuals and species.

Furthermore, some of these animals repeatedly gassed to complete unconsciousness for short periods with a high concentration of carbon monoxide suffered only slight organic changes in comparison with those subjected to highly diluted carbon monoxide gas for from one to several hours at a time. This confirms the observations of Nicloux[36] that

35. Douglas, C. G.; Haldane, J. S., and Haldane, J. B. S.: The Laws of Combination of Hemoglobin with Carbon Monoxide and Oxygen, J. Physiol. **44**: 275, 1912.

36. Nicloux, Maurice: L'oxyde de carbone et l'intoxication oxycarbonique: Étude chimico-biologique, Paris, Masson & Cie, 1925.

the changes in the organs depend not on the concentration of carbon monoxide in the blood, but on the length of time of exposure even to small quantities of the gas.

So far as these experiments indicate, rabbits are especially resistant to carbon monoxide, judging by the few lesions after so many and such long exposures. That there is a great difference in the hemoglobin's affinity for carbon monoxide and for oxygen in various species and also in the various individuals of a species has also been demonstrated by Anson, Barcroft, Mirsky and Oinuma.[37] According to one of their charts, the hemoglobin's affinity for carbon monoxide decreases in various animals and man as follows: Dog, horse, mouse, cat, man, fowl, rat, tortoise, sheep, lizard, roach, frog and rabbit. They also noticed a difference in individual rabbits. In experiments carried out in the Bureau of Mines, Burrell and Seibert[38] found that with 0.25 per cent carbon monoxide a small dog was in distress within fifteen minutes, but a rabbit showed no distress after two hours and twenty minutes. Guinea-pigs gave variable results, some showing distress within from ten to twenty-two minutes, while one was only slightly affected in two hours and another not at all after four hours.

The symptoms in the animals in these first experiments were defecation and urination immediately before loss of consciousness took place. In the rabbits there was furthermore a fleeting paralysis of the hind legs, lasting from five to fifteen minutes. The dogs were dazed and helpless from thirty to forty minutes after each gassing, tottering about as if intoxicated, and there was repeated vomiting during and after each experiment, nor would they partake of food for several hours afterward. The guinea-pigs suffered only rarely a fleeting paralysis of the hind legs, never lasting more than from four to eight minutes. All the rodents ate voraciously immediately after recovery. That no clinical symptoms were observed in the first series of our experiments may have been due to the quantities of gas used, 480 cc. being the maximum that could be administered intra-abdominally without too much distention. Lewin claimed that 500 cc. of carbon monoxide is necessary for intra-abdominal injections to produce symptoms of poisoning in a rabbit. In the second experiment made to ascertain the rate of elimination, marked difference in the metabolism of the dogs as compared with rodents was noted. Whereas in the former there was a loss of weight

37. Anson, M. L.; Barcroft, J.; Mirsky, A. E., and Oinuma, S.: On the Correlation Between the Spectra of Various Hemoglobins and Their Relative Affinities for Oxygen and Carbon Monoxide, Proc. Roy. Soc., London **97**:61, 1924.

38. Burrell, G. A.; Seibert, P. M., and Robertson, I. W.: Relative Effects of Carbon Monoxide on Small Animals, Bureau of Mines Technical Paper 62, 1914.

of from 4 pounds 2 ounces to 9 pounds 2 ounces (1.85 Kg. to 4.15 Kg.), according to their size, in the rabbits the decrease of weight after a much longer period of gassing was only from 8 ounces (0.2 Kg.) in one to 1 pound (0.5 Kg.) in another, and two rabbits preserved their normal weight throughout the experiments. Of the three guinea-pigs, one showed a reduction of 1 ounce (0.025 Kg.) in weight. This marked loss of weight in the dogs may be attributed to their frequent vomiting during and after each experiment. Another explanation has been offered by Glaubitz,[39] who also noticed a decreased weight in his animals after thirteen days and found that the elimination of nitrogen far exceeds the intake of nitrogen from the food. He also mentioned a number of other investigators who found a definite increase in the destruction of protein during their experiments with carbon monoxide.

Apparently with the exception of the experiments by Klebs,[17] neither illuminating gas nor any of its components has been injected directly into the common carotid artery of animals. An attempt was therefore made by one of us (L. H. B.) to determine the nature of the changes produced in the brains of animals with the injection of pure carbon monoxide into one of the common carotid arteries.[40] For this purpose, dogs were used, and carbon monoxide was generated by the action of a few cubic centimeters of formic acid (85 per cent) on 10 cc. of concentrated sulphuric acid.[41] The gas was passed through a soda lime absorption tube, the first 250 cc. discarded, and the rest collected, by displacing water, in 50 cc. glass tubes. These tubes, after the rubber connections were tightly clamped, were stored under water so that any leak would be readily detected. This method of making carbon monoxide has the advantage that relatively small quantities, from 1 to 2 liters, are obtained without admixture of carbon dioxide. This gas was analyzed for its air content by the Haldane method[27]; 1.2 per cent of air was present. The amount desired for injections was drawn into a sterile syringe by displacing the carbon monoxide in the tube with sterile water.

Under ether anesthesia, and with measures to secure asepsis, the left common carotid artery of dogs was isolated and carbon monoxide injected; some dogs were given a mixture of equal parts of air with carbon monoxide. Five of the sixteen dogs receiving carbon monoxide exhibited symptoms. Their character and severity apparently were related to a ratio between the amount of carbon monoxide injected and

39. Glaubitz, G.: Ueber Eiweisszerfall bei Vergiftungen, Ztschr. f. d. ges. exper. Med. **25**:230, 1921.

40. Dr. G. Rukstinat assisted me in these operations. L. H. B.

41. Nicloux (footnote 35, p. 23).

the weight of the animal. Undoubtedly, the amount of hemoglobin in the animals bore some definite relation to weight. Several cubic centimeters, e. g., 6, caused symptoms in a small, but not in a heavier dog. Convulsions occurred a few hours after the injection. They were preceded by marked restlessness and irritability, the animal running aimlessly about, then becoming listless and finally lying down. Then, without bark or warning cry, convulsions appeared, with the head thrown back and the back arched. When the animal stood up on his hind legs, he was thrown over on his back, where he lay panting and jerking spasmodically. Sometimes such symptoms were accompanied by a running motion of the front legs, as many as one hundred movements being made a minute, the hind legs quiet, spastic and stretched out straight. A convulsion lasted several minutes and was followed by quiet exhaustion and dyspnea, the animal lying on one side. Then another convulsion developed. As one after another took place, their duration lessened to half a minute. Alternating with the periods of exhaustion, the convulsions continued in some animals for from two to twelve hours, or until death. During the convulsions the animals were unconscious. After such attacks as these, none of the animals recovered. The symptom in one animal was simply a belligerency not previously shown and disappearing altogether after ten days. Another walked exclusively to the right shortly after the operation, but only for a few hours and the next day was normal. In a third, the only trouble seemed to be muscular weakness, which came on eight days after the gas was injected. The gait was unsteady and the animal was prone to fall to one side or the other.

So far as known, the death of one dog was not accompanied by convulsions. This death occurred twenty-four hours after a second injection with an interval of eleven days between it and the first. When this second injection was made, bubbles of gas were seen in the adjacent jugular vein, as well as in all the other veins exposed by the operation. After death, the lining of the rectum was deep purple, and minute, bright red hemorrhages were found in the epicardium at the apex and ventrally, in the superficial substance of the liver and in the papillary muscles of the mitral leaflets.[42] Alternating bright red and dark purple blood in the coronary veins gave them a beaded appearance.

In two other dogs, gas bubbles were noted in the adjacent jugular vein. One was killed several hours after the injection of carbon mon-

42. A number of observers (see Gey, R.: Zur pathologischen Anatomie der Leuchtgasvergiftung, Virchows Arch. f. path. Anat. **251**:95, 1924) have noted these hemorrhages in the heart. They are probably mechanical and associated with the dilation of the heart, as well as with dilation of the small vessels where bleeding occurs.

oxide. The capillaries in the anterior papillary muscle of the mitral leaflets were distended. The other dog was killed seven days after the administration of pure carbon monoxide. One dark, well circumscribed hemorrhage, 1.5 mm. in diameter, was on the convex surface of the right lobe of the liver. In a dog dying from six to fifteen hours after the injection and in the one with distended capillaries in the papillary muscle, the smallest arteries and veins in the pia mater contained globules of gas.

Hyperemia of the outside of the brain was present in dogs dying from six to eight hours after injection or in those killed from three to seven days later. The veins were markedly distended and filled with dark red blood, especially the middle cerebral veins. Over the entire brain the smallest ramifications of the blood vessels were distinct. Only one brain was a bright cherry red. It came from the dog dying from six to fifteen hours after receiving carbon monoxide; during the hours before death, there were many severe convulsions. A few hemorrhages, from 2 to 5 mm. in diameter, in the pia mater were also noted, with hyperemia on each side, more along the top, not far from the longitudinal fissure and a few centimeters posterior to the frontal poles. A few were found over the occipital lobes, often in the most posterior portion. These hemorrhages were well defined and a dusky reddish brown.

With the hyperemia and hemorrhages in the pia mater there was pronounced stippling of the surfaces of segments made by coronal sectioning; the stippling was fairly symmetrical and more prominent in the white matter. In about one half of the brains there were also punctate hemorrhages in the white matter and cortex, the larger ones usually in the gray matter, and 1.5 mm. in diameter. In dogs dying within twenty-four hours, the hyperemia was more marked on the side of injection. One dog killed after three days showed: engorgement of blood vessels with punctate hemorrhages in the white matter, cortex, caudate nuclei and thalamus; a diffuse grayish-brown color throughout the left lenticular nucleus; scattered similar regions of discoloration in the right nucleus; one brown discoloration in the ventral tip of the left caudate nucleus; and an extremely dark gray area in the cortex, lateral to the right thalamus, with numerous distended blood vessels about it. In another brain there was a region of punctate hemorrhages in the middle of the left caudate nucleus. The surfaces of the cerebellum, pons, medulla and regions of the substantia nigra were frequently peppered with engorged blood vessels and occasional hemorrhages. In the medulla of one dog there were four small hemorrhages.

The caudate nuclei of normal dogs stand out as well defined regions. One change of particular interest in seven of the sixteen brains was a partial or total loss of this sharp demarcation. This was observed from three to ten days after the injection of carbon monoxide. In the more anterior sections of the brain, the heads of the caudate nuclei were white and readily distinguished from the remaining gray portion, but posteriorly the nuclei were colorless and the boundary between them and the adjacent white matter was indefinite. This alteration was always bilateral, although more on one side as a rule. It was the only change found in the brain of one dog killed after the injection of 5 cc. of carbon monoxide. A similar discoloration of the gray substance of the thalamus occurred in a few dogs; in one it was complete on both sides; in the others, there was simply a vague external boundary.

The lenticular nuclei normally varied in color from pale gray to yellow. In the left lenticular nucleus in the brain from one dog there was a cavity, while in the right one there were three, those in the right side being farther anterior. These were round or oval and from 1 to 3 mm. in diameter; the immediately adjacent brain substance was creamy white. The left lenticular nucleus appeared to be connected with the caudate nucleus by a friable band of tissue traversing the middle of the internal capsule. In another brain there was a fragmented, depressed, reddish-brown region bounding the caudate nuclei and extending laterally to the ventricle. On the left side, the anteroposterior length was 8 mm.; on the right, 7.5 mm. The gray matter of the lenticular nuclei was poorly defined in the brains from some dogs killed eight days or later after injection. In a third brain there was a well circumscribed soft, gray region, several millimeters in diameter, external to the right lenticular nucleus, with similar softenings outside both thalami (fig. 2). In a fourth brain there were cavities or soft places the consistency of curdled milk, from 1.5 to 6 mm. in diameter, in the white substance outside each lenticular nucleus and, on one side, extending down into, or close to, Ammon's horn.

In a fifth brain were found two small cavities in the cortex, a few millimeters in diameter, and several to the right of the midline in the coronal segments that included parts of the thalami. They were empty, had ragged walls and were connected by a narrow bridge of friable cortex. In another dog killed twenty-four days after the injection of carbon monoxide, the only gross change was a soft cortex of the left occipital lobe, not well demarcated from the normal adjacent tissue. No gross changes were discovered in the brains of three dogs receiving 3.5, 5 and 15 cc. of carbon monoxide and killed after six, nine and sixteen days, respectively.

The acute distention of blood vessels in all organs of the body following the breathing of illuminating gas has been attributed to the carbon monoxide in the gas. Since this evidently occurs in the lungs, hemorrhages being commonly seen in the lungs of persons who die from carbon monoxide, the question arose whether the poisonous gases containing carbon monoxide or mixtures of such gases with air may enter the blood stream directly through minute lacerations in the vessels and pass along into the circulation by the pulmonary veins as emboli. Such emboli of air with carbon monoxide, perhaps, are swept into the general circulation so as to plug the small arteries in the brain. On the morning following the injection of an equal mixture of carbon mon-

Fig. 2.—A coronal section 27 mm. posterior to the frontal poles in the brain from a dog dying twelve hours after the introduction of 15 cc. of carbon monoxide. The stippling is marked. The letter *a* indicates the grayish-white left caudate nucleus; *b*, distended blood vessels in the right caudate nucleus, and *c*, softening in the cortex lateral to the right lenticular nucleus. These softenings are bilateral, but not always at the same front-to-back level.

oxide with air, one dog lay in his cage, all four extremities stretched out straight; the respirations were shallow and rapid. No one saw the dog during the night, so that it is not known whether there had been convulsions. The dog was killed about twenty-two hours after the operation. The outside of the brain was hyperemic, but except for engorged vessels in the frontal lobes and the left lenticular nucleus the substance was normal grossly. In another dog, a similar mixture caused no disturbance. This dog was killed four days later. There was marked hyperemia in all of the coronal surfaces made by sectioning the brain.

Above the left caudate nucleus were two small cavities, 1 mm. in diameter, spherical and smooth inside; in the left occipital lobe were two extremely soft regions in the white matter, with anteroposterior diameters of 9 to 20 mm., the longer extending to the most posterior portion of the cerebrum.

It has been suggested that the convulsions which occasionally are seen in whooping cough are caused by air embolism,[43] that during such severe spasms of coughing the lung capillaries are torn by the great intrapulmonic pressure and air enters the pulmonary veins. Husler and Spatz [44] described degenerative changes in the cortex, especially that of the cornu ammonis, in the brains of children dying of whooping cough, and similar cortical damage in criminal abortion [45] has been ascribed to air embolism of the brain. For these reasons, control experiments were made by injecting air into one carotid artery in dogs. More pressure is required to force air into circulating blood than is needed with carbon monoxide. Air tends to enter spasmodically, and the artery for a time remains distended and colorless. With carbon monoxide, the blood column remains continuous, and no gas is visible.

In three of six dogs receiving air, convulsions occurred. Following a shrill cry, the head was thrown forcibly backward, and there was a rapid running movement in the fore legs. In one dog, only the right fore leg had this movement. The hind legs were, as a rule, motionless, but occasionally irregular, purposeless movements took place. With 10 cc. of air, the convulsions were severe, and usually death followed in from two to seven hours. In one dog, 10 cc. produced no symptoms; in another, marked restlessness. Smaller amounts of air (5 cc.) caused convulsions in some of the dogs and death from five to ten hours later. Dogs in which convulsions were produced died. With death after several hours, most of the blood vessels in the leptomeninges were beaded with air. In one brain, this was so pronounced that there was little blood left in the pial vessels. The air was in the smallest arteries, as well as in the veins, and either equally distributed on both sides or more on the side of injection.

In one brain, a lesion similar to those following the injection of carbon monoxide was in the outer portion of one thalamus; also a small

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43. Neubürger, K.: Ueber cerebral Fett- und Luft- Emboli, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:278, 1925.

44. Husler, J., and Spatz, H.: Die Keuchhusten-Eklampsie, Ztschr. f. Kinderh. **38**:428. 1924

45. Weimann, W.: Gehirnbefunde bei septischer Allgemeininfektion (nach kriminellen Abort), Ztschr. f. d. ges. Neurol. u. Psychiat. **11**:242, 1928. Spielmeyer, W.: Ueber die anatomischen Folgen der Luftembolie ins Gehirn, Verhandl. d. Kong. f. inn. Med. **30**:359, 1913.

dark hemorrhage, several millimeters in diameter, was in the left dentate nucleus. In another, disseminated punctate hemorrhages were in the cortex and white matter of all the coronal segments. The last two dogs had no convulsions and were killed after ten and fourteen days, respectively. In a third dog dying about six hours after the injection of air, one solitary bright hemorrhage, several millimeters in diameter, was in the cortex near the top of the brain. In another dying after eight hours, a soft region was found in the cortex of the left side, at the level of the thalamus. In the fifth there was softening in the cortex. The sixth dog lived fourteen days after receiving 10 cc. of air, and the brain was unchanged.

CONCLUSIONS

These experiments demonstrate that the effect of carbon monoxide varies in different animals; that it is rapidly eliminated by rabbits and guinea-pigs; that rabbits are especially resistant to the gas, and that the weight of the animals, the amount of the gas and the manner of administration modify its action.

Symmetrical lesions in the brains of the dogs and more rarely in those of guinea-pigs and rabbits, lesions resembling those occasionally found in human brains, may be produced experimentally by injecting the gas into the arterial blood stream or by having the animals inhale pure carbon monoxide, or illuminating gas.

When pure carbon monoxide is injected into the blood stream, it combines so rapidly with the hemoglobin that gas embolism does not occur, or at least not with doses such as were injected in these experiments.

Ten cubic centimeters of air alone injected into the carotid arteries of dogs causes severe convulsions, is more frequently and speedily fatal than a similar amount of carbon monoxide, and results in fewer gross changes, these being rarely in the basal ganglions.

A STANDARDIZED PROCEDURE SUGGESTED FOR MICROSCOPIC STUDIES ON THE HEART

WITH OBSERVATIONS ON RHEUMATIC HEARTS *

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It is exceedingly difficult at present to compare statistical data reported in various histologic studies of pathologic hearts. The principal difficulty seems to be due to the fact that the changes are often reported without consideration of their exact location in the heart. For example, the discrepancies in the reported incidence of Aschoff bodies, myocardial softening or scarring, vascular lesions, inflammatory foci, etc., may to a considerable extent be accounted for both by the difference in the number of sections studied by the various workers and by the difference in the sites from which the tissues were removed.

In the course of examining a large number of human hearts, we have developed a simple procedure for cutting tissues, which it is believed shows a maximum number of lesions in a minimum number of blocks of tissue. These blocks are cut from definite topographic sites in the heart and are so designed that each block includes certain "strategic" sites, i. e., areas which experience has shown are frequently the seat of disease. It is not suggested that investigators confine themselves to the study of these blocks only. They could be considered to advantage, however, as a sort of common denominator for the purpose of statistical comparisons.

We shall present the method that we employ, with a brief histotopographic description of the more important structures to be found in each section. In this description, it will be necessary to use a terminology that may be unfamiliar or, indeed, in some instances new. We believe it advisable, however, that some such terminology be adopted in order to avoid confusion in the future.

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* From the Laboratories of the Mount Sinai Hospital.

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In order to illustrate the advantages of the different sections, we shall indicate the relative incidence of vascular lesions (arteriosclerotic), myocardial scarring and Aschoff bodies in each area as found in a study of thirty-seven rheumatic hearts, all of which contained Aschoff bodies.

METHOD

It is desirable that at least two sections from each block be stained, one with hematoxylin and eosin and the other with some good stain for differentiating elastic and fibrous connective tissue, such as Weigert's stain for elastic tissue and van Gieson's for fibrous tissue, or Weigert's for elastic tissue and Masson's erythrosin-saffron, etc. We seldom employ the Unna-Pappenheim methyl-green-pyronin stain, as this often leads to greater confusion. From time to time it will be necessary to use a good bacterial stain, such as the MacCallum-Goodpasture or azure-B; also a stain for fibrin, such as Weigert's, or Mallory's phosphotungstic hematoxylin.

Before the blocks are cut, the heart should be fixed in a neutral formaldehyde sodium chloride solution [1] or a formaldehyde solution of Mueller.[2] If the tissues are fresh (less than six hours post mortem), Bouin's fluid will be found excellent. For special purposes, small blocks may be immediately fixed in alcohol.

The heart is opened in the customary manner, and after fixation the following blocks are cut: (1) left auricle (L. A.) [3]; (2) mitral posterior (M. P.); (3) posterior papillary muscle, left (P. P. M.); (4) aorta, aortic valve and mitral valve (A. M. V.); (5) pulmonary artery and valve (P. A. V.), and (6) tricuspid valve and septum (T. V.).

In the following descriptions, when referring to "left" or "right" we have in mind the *anatomic* "left" or "right" of the heart. As far as possible the terminology of Basle Nomina Anatomica will be used.

Left Auricle (L. A.).—With a pair of scissors, a transverse cut, approximately 3 cm. in length, is made from the posterior cut border of the left auricle toward the interauricular septum approximately 1 cm. above the insertion of the posterior flap of the mitral valve (fig. 1). A cut is made parallel to this, approximately 3 mm.[4] above the first. The right border of the narrow slab is severed with a knife.

Histotopographically (fig. 2), this section shows: the left auricular endocardium (*A*), the left auricular subendocardium (*B*), the left auricular myocardium (*C*), the pericardium (*D*) and sometimes, the coronary sinus (*E*).

Mitral Posterior (M. P.).—Starting from the slot from which the left auricular section was removed, a vertical cut is made with a scalpel downward toward the apex of the heart so that the blade passes through the posterior leaflet of the mitral valve and the subjacent myocardium (through its entire thickness) at

1. Solution of formaldehyde, U. S. P., 10 parts; 1 per cent sodium chloride solution, 90 parts. This solution is rendered neutral with a weak alkali.

2. The formaldehyde solution of Mueller (Formol-Mueller) is prepared as follows: potassium bichromate, 2 parts by weight; water, 100 parts; solution of formaldehyde, U. S. P., 10 parts. The "solution of formaldehyde" is added just before use.

3. The letters in brackets are convenient abbreviations for designating the sections on the slide.

4. All slabs are cut about 3 mm. thick.

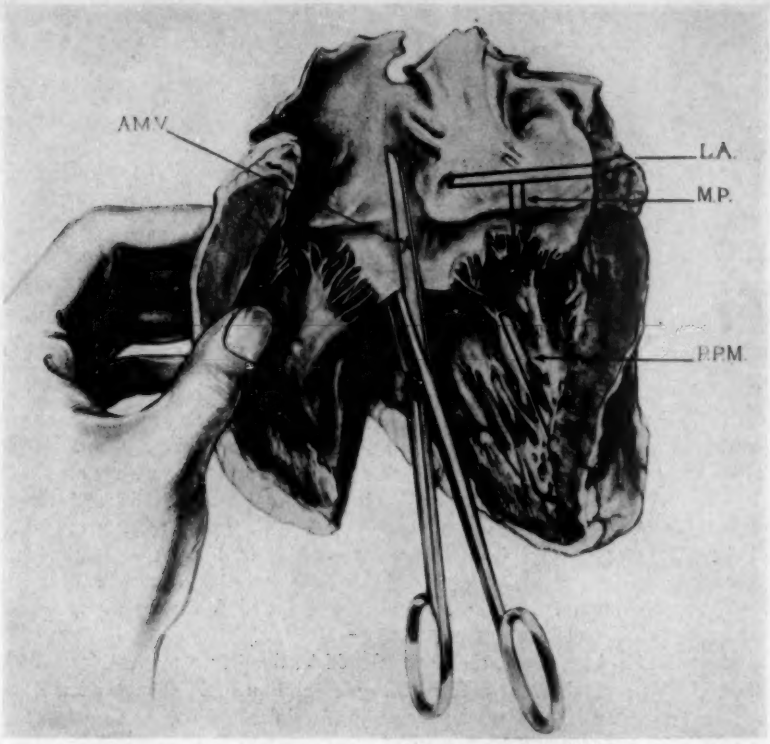

Fig. 1.—Diagram of left auricle and ventricle (left inflow tract) showing the method of cutting the left auricle, mitral posterior, left posterior papillary muscle, and aorta, aortic valve and mitral valve blocks.

Fig. 2.—Low power magnification of left auricle (L. A.) section. *A* indicates the left auricular endocardium; *B*, the left auricular subendocardium; *C*, the left auricular myocardium; *D*, the pericardium, and *E*, the coronary sinus.

about the region indicated in figure 1. The cut is carried through the myocardium to about 3 mm. below the free edge of the valve. A parallel cut is then made and the block removed in the usual manner.

Histotopographically (fig. 3), this section shows: Left auricular endocardium (*A*). Left auricular subendocardium (*B*). Myocardial wedge of the

Fig. 3.—Low power magnification of mitral posterior (M.P.) section. *A* indicates the left auricular endocardium; *B*, the left auricular subendocardium; *C*, the left auricular myocardial wedge; *D*, the pericardial wedge; *E*, the left ventricular myocardium; *F*, the ring of the posterior mitral valve; *G*, the posterior leaflet of the mitral valve, and *H*, the posterior mitral pocket.

left auricle (*C*). Note that this inserts into the mitral ring. Pericardial wedge (*D*). Note the intimate relation between the pericardial wedge and the mitral ring. Left ventricular myocardium (*E*).

The ring of the posterior mitral valve (*F*). It is rather difficult to define accurately the region that we desire to indicate by the term "ring." In this section, it consists of a small area of fibrous tissue into which there is inserted the auricular myocardial wedge, the pericardial wedge and the base of the valve.

The posterior leaflet of the mitral valve (*G*).

The posterior mitral pocket (*H*), i.e., the tissue lying immediately above, and surrounding, the upper part of the cleft between the valve flap and the endocardium of the left ventricle.

Sometimes, the coronary sinus.

Fig. 4.—Low power magnification of the posterior papilary muscle, left (P.P.M.) section. *A* indicates the myocardium; *B*, the endocardium, and *C*, the insertion of the chorda tendineae.

Posterior Papillary Muscle, Left (P. P. M.).—A longitudinal incision is made with a scalpel, starting at the apex of the posterior papillary muscle (when the posterior papillary muscle is forked, the right fork should be used) and continuing down into the base (fig. 1). A parallel incision is then made in the usual way and the block removed.

Histotopographically (fig. 4), this section shows: the myocardium of the left posterior papillary muscle (*A*), the endocardial covering (*B*) and, sometimes, the insertion of the chordae tendineae (*C*). This section is valuable in the study of vascular lesions, infarction, fibrosis, Aschoff bodies, etc.

Aorta, Aortic Valve and Mitral Valve (A. M. V.).—The section including the aorta, aortic valve and mitral valve is one of the most valuable in the series. The anterior segment of the left ventricle is grasped by the left hand (fig. 1). A pair of scissors is inserted beneath the anterior flap (aortic) of the mitral valve

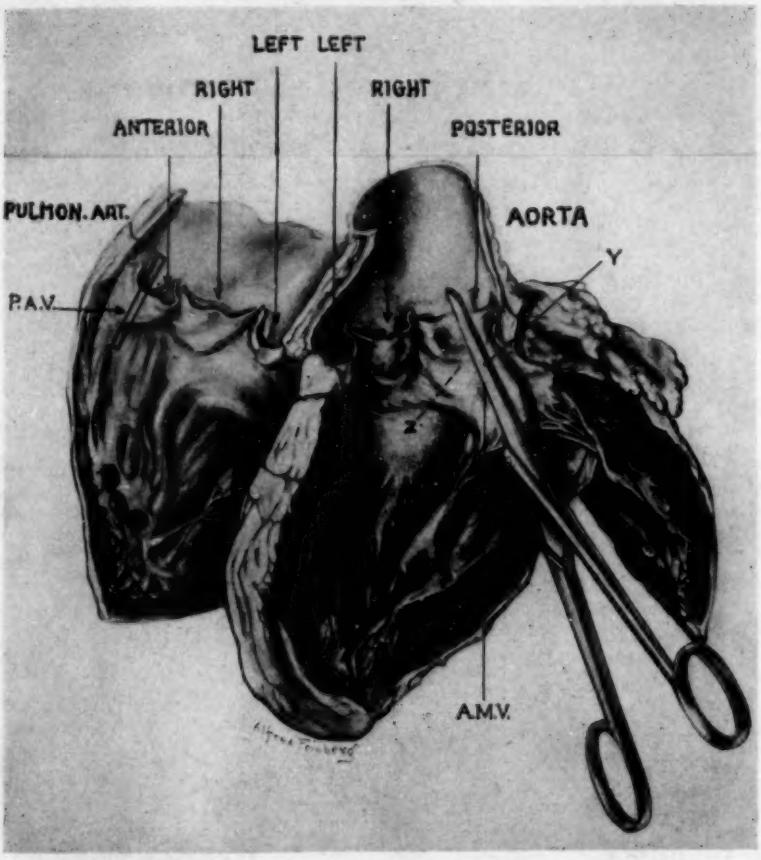

Fig. 5.—Diagram of the left and right ventricles (outflow tracts), showing the method of cutting the aorta, aortic valve and mitral valve (A.M.V.) and the pulmonary artery and valve (P.A.V.) blocks.

so that one blade (*X*) lies against the auricular surface of the aortic flap of the mitral valve and the other blade (*Y*, fig. 5) lies against the posterior (non-coronary) cusp of the aortic valve. This incision is carried upward through approximately the middle of the posterior cusp of the aortic valve and through the lower portion of the aorta. A narrow parallel incision is made and the block removed.

Histotopographically (fig. 6), this section shows: Left auricular endocardium (*A*). Left auricular subendocardium (*B*). Left auricular myocardial wedge (*C*). Pericardial wedge (*D*). The root of the aorta (*E*). The aortic valve (*F*). The sinus pocket (*G*), i.e., the junction between the base of the aortic valve and the base of the aorta.

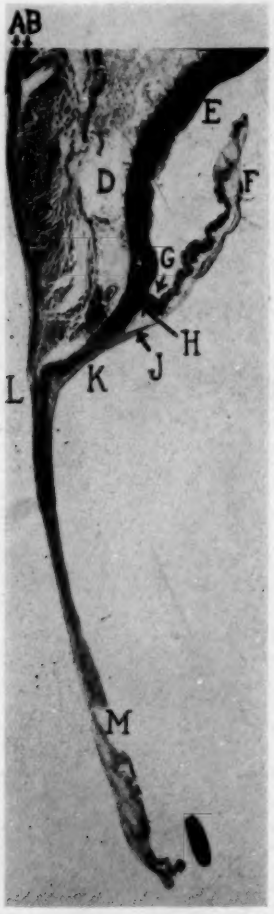

Fig. 6.—Low power magnification of the aorta, aortic valve and mitral valve (A.M.V.) section. *A* indicates the left auricular endocardium; *B*, the left auricular subendocardium; *C*, the left auricular myocardial wedge; *D*, the pericardial wedge; *E*, the root of the aorta; *F*, the aortic valve; *G*, the sinus pocket; *H*, the aortic ring; *J*, the subaortic angle; *K*, the mitral-aortic intervalvular fibrosa and endocardium; *L*, the mitral ring, and *M*, the anterior or aortic flap of the mitral valve.

The aortic ring (*H*). This consists of a triangular area of connective tissue the base of which rests on the subjacent pericardium and the apex of which merges imperceptibly with the base of the valve.

Subaortic angle (*J*). By this term is meant that portion of the endocardium that lies at the junction of the base of the aortic valve on its ventricular aspect and the continuation of the mitral valve on its ventricular aspect.

Mitral-aortic intervalvular fibrosa and endocardium (*K*), i.e., that portion of fibrous tissue and endocardium the upper limit of which is the aortic ring, the left border of which abuts against the auricular pericardium and the lower limit of which is on a level with the tip of the auricular myocardial wedge (mitral ring).

Mitral ring (*L*). This is rather an ill defined area corresponding to the insertions of the aortic flap of the mitral valve into the mitral-aortic intervalvular fibrosa and left auricular myocardial wedge.

Aortic flap of the mitral valve (*M*).

Pulmonary Artery and Valve (P. A. V.).—Before this section is described, it is advisable to state the terminology of the aortic and pulmonary cusps. The aortic cusp corresponding to the ostium of the right coronary artery is called the

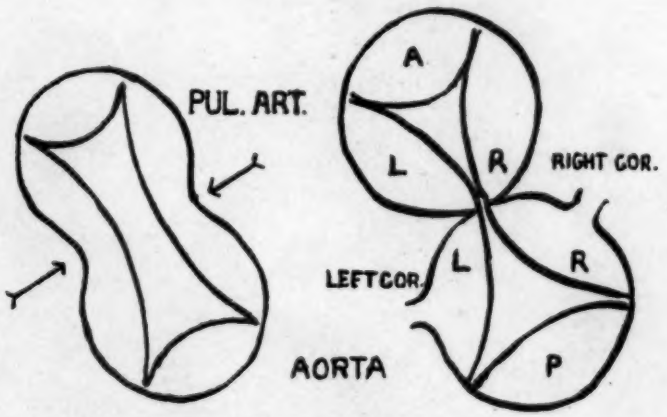

Fig. 7.—Diagram of the embryogenesis of the pulmonary artery and the aorta, illustrating the relationship of right-left pulmonary commissure (R.L.) to the right-left aortic commissure (R.L.). *L* = left; *R* = right; *P* = posterior; *A* = anterior; *Cor.* = coronary artery.

right cusp (figs. 5 and 7). That corresponding to the ostium of the left coronary artery is called the left cusp. The noncoronary cusp is called the posterior cusp. This affords a simple terminology for the commissures; thus, the commissure between the right and left cusps is called R. L. commissure (right-left commissure). That between the right and posterior cusps is called R. P. commissure (right-posterior commissure). That between the left and posterior cusps is called L. P. commissure (left-posterior commissure).

The terminology of the pulmonary cusps is somewhat more difficult to define because of the absence of coronary ostia, but a brief consideration of the embryogenesis of the semilunar cusps gives an excellent landmark for this purpose. At one stage in the evolution of the aortic bulb before the pulmonary artery and the aorta have separated from one another, the semilunar cusps are represented by four endocardial cushions. At the points marked by the arrows in figure 7, a constriction takes place that eventually separates the two vessels. It will be

easily seen from this that only two commissures, one from each vessel, remain in juxtaposition. That on the aortic side is the R. L. commissure. That on the pulmonary side opposite the aortic R. L. commissure separates the right pulmonary cusp from the left pulmonary cusp [5] (fig. 5). The remaining pulmonary cusp is called the anterior.

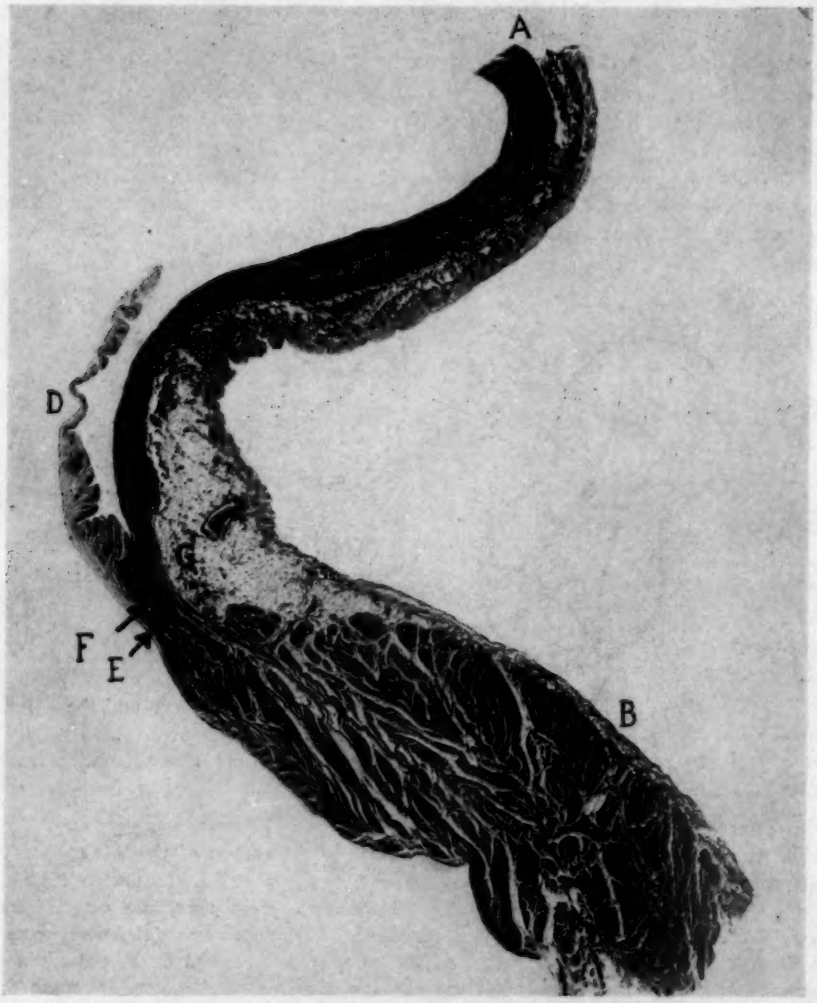

Fig. 8.—Low power magnification of the pulmonary artery and valve (P.A.V.) section. *A* indicates the pulmonary artery and investing pericardium; *B*, the pericardium of the right ventricle; *C*, the pericardial wedge; *D*, the pulmonary valve; *E*, the subpulmonic angle; *F*, the pulmonary ring, and *G*, the right ventricular myocardium.

5. The close apposition of these two commissures is not brought out in the schematic drawing, figure 5.

It is obvious that by carrying out the same scheme as was suggested for the aortic valve, a simple terminology with regard to the pulmonary commissures also becomes available.

With a pair of scissors, a cut is made transversely, starting at the right cut border of the pulmonary artery several millimeters above the free edge of the anterior cusp of the pulmonary valve. When the incision reaches approximately opposite the middle of this cusp, the scissors are turned downward, i.e., toward the apex of the heart, and an incision is made through the base of the pulmonary

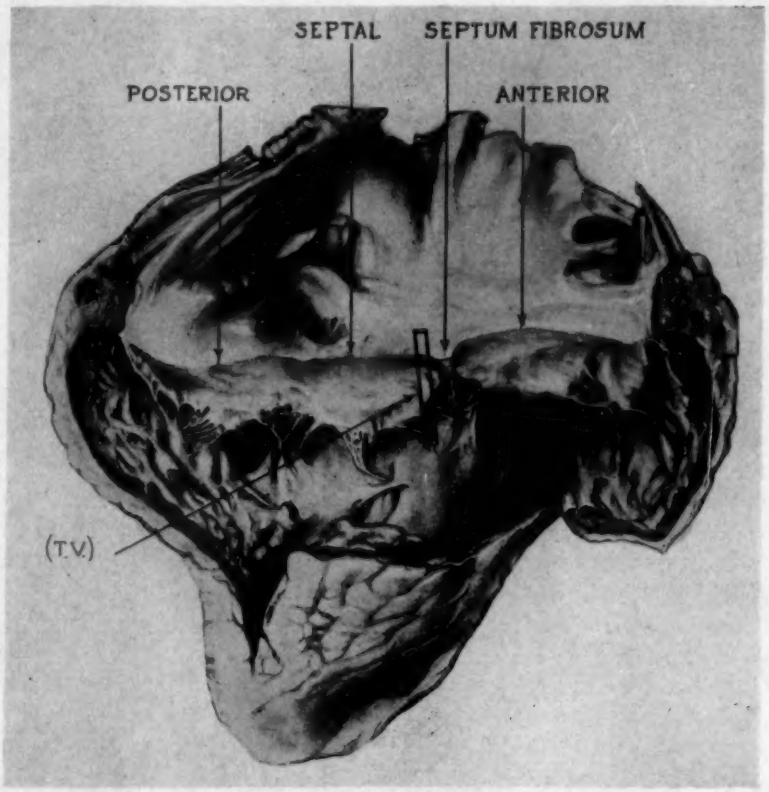

Fig. 9.—Diagram of the right auricle and ventricle (right inflow tract), showing method of cutting the tricuspid valve and septum (T.V.) block.

artery, the anterior pulmnary cusp and the right ventricular myocardium to approximately 1 cm. below the base of this pulmonary cusp. Another vertical incision is made parallel to the latter incision and the block removed.

Histotopographically (fig. 8), this section shows: the pulmonary artery and investing pericardium (*A*), the pericardium of the right ventricle (*B*), the pericardial wedge (*C*), the pulmonary valve (*D*), the subpulmonic angle (*E*) (corresponding to the subaortic angle), the pulmonary ring (*F*) (corresponding to what was described for the aortic ring) and the right ventricular myocardium (*G*).

Tricuspid Valve and Septum (T. V.).—For purposes of completeness, the terminology of the tricuspid cusps and their commissures will be briefly stated. The flap that lies over the interventricular septum and is situated below the coronary sinus is called the median or septal flap (fig. 9). The free flap anteriorly to its left is called the anterior flap. The remaining flap is called the posterior flap. It will be noted that the commissure or junction between the septal flap and the anterior flap lies in close proximity to the undefended space (septum fibrosum). This commissure is called the septal-anterior commissure (S. A. commissure). Similarly, the commissure at the right extremity of the septal

Fig. 10.—Low power magnification of the tricuspid valve and septum (T.V.) section. *A* indicates the right auricular endocardium; *B*, the right auriclar subendocardium; *D*, the neuromuscular bundle; *E*, the septum fibrosum; *F*, the tricuspid ring; *G*, the tricuspid valve; *H*, the interventricular septum, and *J*, the tricuspid pocket.

flap is called the septal-posterior commissure (S. P. commissure). The remaining commissure is called the anterior-posterior commissure (A. P. commissure).

The section with which we are about to deal is cut from the region of the septal anterior commissure. The point of the scalpel is inserted through the right auricle at a point approximately 1 cm. above the insertion of the septal flap and 5 mm. to the right of the septal-anterior commissure (fig. 9). The

point of the knife is pushed through so that it emerges generally below the posterior cusp of the aortic valve (dotted line *Z*, fig. 5). The blade is then carried down toward the apex, through the right auricle, the septal cusp of the tricuspid valve and the subjacent interventricular septum to a point approximately 1 cm. below the free edge of the septal cusp. A parallel incision is made approximately 3 mm. to the left of the original cut. The block is removed.

Histotopographically (fig. 10), this section shows: Right auricular endocardium (*A*). Right auricular subendocardium (*B*). Right auricular myocardium (*C*).

Neuromuscular bundle (*D*). Note that the removal of this block does not in any way interfere with complete serial sections of the conduction system, since the block constitutes a segment of the standard vertical blocks cut for such purposes.

Septum fibrosum (*E*). Tricuspid ring (*F*.) (corresponding to what was described for posterior mitral ring). Tricuspid valve (*G*). Interventricular septum (*H*). Tricuspid pocket (*J*) (corresponding to what was described for posterior mitral pocket). Occasionally, a portion of the aortic valve.

If it is desired to include in this section the pericardial wedge opposite the tricuspid ring, a section may be taken from the septal cusp of the tricuspid valve closer to its right extremity.

COMMENT

It will be seen from this brief description that these six blocks include the following important sites in the heart: all four valves; all four valve rings; the pericardium of the left and right sides of the heart (represented in four sections); the left and right auricles; the myocardium of the left ventricle, right ventricle, interventricular septum and left posterior papillary muscle; the bases of the aorta and pulmonary artery; the pericardial wedges abutting against the valve rings; the neuromuscular bundle, and the coronary sinus.

It will be noted that the myocardium in practically every section is taken from a site where the vessels can be considered end-vessels, i. e., the tip of the left and right ventricles and the interventricular septum. It is probably for this reason that early vascular changes and their results are so frequently observed in these sections, and that inflammatory lesions, which may possibly owe their localization to the fact that the vessels in this region are terminal, are so frequently found here.

It will also be noted that the left auricle is represented by three sections. The possibility of studying rheumatic lesions and arteriosclerotic changes in this region at once becomes apparent.

As we stated before, this paper is concerned chiefly with the description of the technic employed. However, in order to illustrate the advantages of this method, we may mention the fact that by using these sections only, we have been able to find Aschoff bodies in 90 per cent of forty hearts showing acute verrucous endocarditis [6] and in 15 per

6. We have considered "verrucous material before fibrosis has taken place" as our criterion for acute verrucous endocarditis.

cent of thirty-nine hearts showing chronic valvular disease. In some of the hearts not showing these lesions, sections from other parts were taken, as well, but failed to show Aschoff bodies. It may be assumed, therefore, that if Aschoff bodies are present, they will be found in the standard sections in the great majority of cases.

The relative incidence of vascular lesions (arteriosclerotic), myocardial scarring and Aschoff bodies in these sections from thirty-seven human hearts, all of which showed Aschoff bodies, is listed in the table. It becomes obvious at a glance that, as judged by these sections, the mitral posterior block (M. P.) and the tricuspid valve and septum block (T. V.) are the most frequent sites for Aschoff bodies. Indeed, if only these two standard sections had been cut, the incidence of Aschoff bodies in our series would have remained the same, as these structures were found in either one or both of these sections in every case in which they were found in the heart.

Incidence of Aschoff Bodies, Scarring and Arteriosclerosis in Thirty-Seven Hearts All of Which Contained Aschoff Bodies *

Site	Aschoff Bodies	Scarring	Arteriosclerosis
Left auricle (L. A.)	10	17	0
Mitral posterior (M. P.)	32	24	4
Posterior papillary muscle, left (P. P. M.)	22	26	11
Aorta, aortic valve and mitral valve (A. M. V.)	9	22	4
Tricuspid valve and septum (T. V.)	30	29	12
Pulmonary artery and valve (P. A. V.)	19	15	0

* Of these hearts, nine were from patients in the first decade of life, sixteen from those in the second, two from those in the third, six from those in the fourth, two from those in the fifth, one from a patient in the sixth and one from a patient in the seventh.

The frequency of scarring in all the sections, except the left auricle (L.A.) and pulmonary artery and valve (P. V.) sections is to be noted, as is also the relative frequency of degenerative vascular changes in the tricuspid valve and septum (T. V.) section and in the posterior papillary muscle, left (P. P. M.) section.

In further publications, we propose to present more detailed observations on various lesions of the heart, and in these publications we hope that the usefulness of this method will be more fully brought out.

SUMMARY

A simple method for the microscopic study of the heart in standard sections is described. The "strategic" sites in each section are briefly reviewed. Their importance is illustrated by some of the observations in thirty-seven cases of rheumatic heart disease. A standard nomenclature is suggested for certain sites in the heart.

ARGENTAFFIN TUMORS OF THE SMALL INTESTINE

A REPORT OF FOUR CASES, ONE WITH METASTASES *

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MADISON, WIS.

Considerable interest has been shown lately in certain tumors of the intestine known as carcinoids, or more accurately as argentaffin cell tumors on account of the affinity for silver of certain granules in their cells. These tumors occur in the small intestine and appendix, sites rarely affected by other primary tumors; they are often multiple in origin; they grow slowly, rarely metastasizing, and they usually give rise to symptoms only by causing intestinal obstruction. Grossly, they are usually small, seldom exceeding 3 cm. in diameter. They are sometimes pedunculated, but often flat and almost embedded in the mucous surface of the intestine. In the appendix, they escape notice grossly, or are in the form of small nodules. The cut surface, whatever the location, is opaque and either gray or yellowish gray. Microscopically, the cells are round or oval, the nuclei round and uniform in size, shape and staining reaction. Mitotic figures are extremely rare. The cells are arranged in more or less solid, coarsely branching groups, with occasional lumen-like spaces. These may be empty or may contain small arteries or merely hyaline material. The pathognomonic intracellular argentaffin granules are usually more numerous on the peripheries of acini. In a cell bordering on a "lumen," the granules are always in the portion of the cell farthest from the opening.

The nature of argentaffin tumors is not thoroughly understood, as a brief review of the widely varying opinions in this regard will show. They were early confused with true carcinomas. Bunting [1] in 1904 called attention to their similarity to basal cell epitheliomas of the skin, in that they are characterized by multiple sites of origin, slow growth and lack of metastases. In 1907, Obernderfer clearly differentiated them from true carcinomas and proposed the name "carcinoid." Saltykow in 1912 and 1913 discussed them in two papers, regarding them as pancreatic island rests.

In 1914, Gosset and Masson [2] discovered the argentaffin nature of the chromaffin (Kulschitzky) cells of the gastro-intestinal tract, and

* Submitted for publication, June 24, 1930.

* From the Laboratory of Pathology, University of Wisconsin.

1. Bunting, C. H.: Multiple Primary Carcinomata of the Ileum, Bull. Johns Hopkins Hosp. **5**:389, 1904.

2. Gosset, A., and Masson, P.: Tumeurs endocrine de l'appendice, Presse méd. **22**:237, 1914.

also the chromaffin and argentaffin characters of carcinoids. In 1928, Masson,[3] by means of serial sections, proved the origin of these tumors from the argentaffin cells of the intestine. This work has been confirmed by several investigators.

In 1925, Forbus [4] reported six cases and reviewed the literature thoroughly. He summed up the important opinions as to the tumors in question thus:

1. The tumors represent true carcinomata derived from the epithelium of the gastrointestinal mucosa.

2. They may be included in the group of basalomata analogous to basal-cell cancers of the skin.

3. They may be malformations belonging to the general group of tumors developing from pancreatic rests, as adenomyoma and accessory pancreas.

4. They may be tumors derived from the chromaffin cells of the crypts of Lieberkühn, and hence be endocrine tumors or tumors of the paraganglionic system.

In view of the limited number of these tumors reported since the discovery of their true derivation, and in view of the fact that one case with metastases is available, it seems profitable to review the cases observed in this laboratory. Unfortunately, the tissue from the case in which metastases occurred and that from one other were fixed in Zenker's fluid. The argentaffin granules stain poorly or not at all after this fixation. An extremely careful morphologic study was made, however, and the histologic features of these tumors were found similar in every respect to those of the proved argentaffin tumors. In fact, in searching for any possible similarity to a true adenocarcinoma, I found that the tumors in question showed less glandlike structure than the tumors in which the argentaffin granules stained clearly (fig. 1). This is contrary to the views of Forbus, who regarded glandlike alveolar arrangement as a differential point on which may rest the diagnosis of adenocarcinoma.

The only other reported case with undoubted metastases was one presented by Gaspar [5] recently. In his case there were mesenteric and hepatic metastases in which the argentaffin granules were stained clearly by both Masson's and Hasegawa's methods. Barth [6] in 1929 reported

3. Masson, P.: Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendix Mucosa, Am. J. Path. **4**:181, 1928.

4. Forbus, W. D.: Argentaffin Tumors of the Appendix and Small Intestine, Bull. Johns Hopkins Hosp. **37**:130, 1925.

5. Gaspar, Istvan: Personal communication to the author concerning a paper presented at the meeting of the American Association of Pathologists and Bacteriologists, New York, 1930.

6. Barth, H.: Untersuchungen am Neuromen und Carcinoiden des Wurmfortsatzes, Virchows Arch. f. path. Anat. **273**:62, 1929.

three cases of appendical carcinoid. In one of these there was metastasis to the ovary. It is possible, however, that this was a direct extension, as the ovary was the right one and apparently had been bound by adhesions that also involved the appendix.

REPORT OF CASES

CASE 1.—At operation for gallbladder disease on a woman, aged 51, a mass, apparently scar tissue, was noted in the mesentery, but was not removed. Forty-eight hours after operation, the patient began to show signs of peritonitis and ileus. Her condition grew progressively worse, and she died four days after operation.

At autopsy, the mass, 5 by 3 by 3 cm., was found to lie in the mesentery of the middle portion of the small intestine. The section surface was soft and

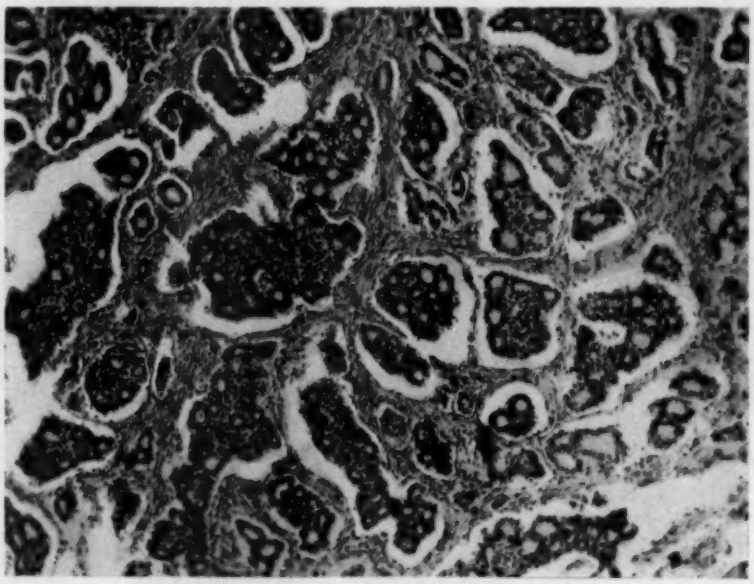

Fig. 1 (case 3).—Argentaffin tumor, showing definite alveolar arrangement of cells; × 80.

hemorrhagic, and a definite fibrous capsule was present. The portion of intestine supplied by the involved mesenteric vessels was gangrenous. For a distance of 30 cm. proximal to the gangrenous portion, the intestinal wall contained irregular nodules. These were in the mucosa and submucosa, most of them being broad and flat and some almost pedunculated. Several mesenteric lymph nodes nearby were enlarged. On the surface of the liver were seven pearly gray nodules, firm and well demarcated. The section surface of the liver also showed several deeper nodules, and all were gray and homogeneous in appearance. There was no evidence of metastasis in any other organ.

Microscopic Examination.—The tumors in the intestine, mesentery and liver were composed of solid masses of tumor cells in alveolar formation. The cells were so crowded together as to obscure cell outlines in most areas, but where

these could be seen they were round or oval. The nuclei were round and uniform in shape and size. No mitotic figures were seen. At several points were structures resembling lumina of glands. Some of these were empty, whereas others contained small blood vessels. The dense stroma in the intestinal tumors was made up partly of fibrous tissue and partly of smooth muscle, but in the mesenteric and hepatic metastases (fig. 2) it was entirely fibrous. It was impossible to stain the argentaffin granules on account of Zenker fixation.

CASE 2.—A woman, aged 71, was admitted to the hospital with symptoms of chronic intestinal obstruction of three months' duration. At operation, an annular tumor, apparently carcinoma, was found constricting the lower part of the ileum. Ileocecostomy was done. The patient died the morning after the operation.

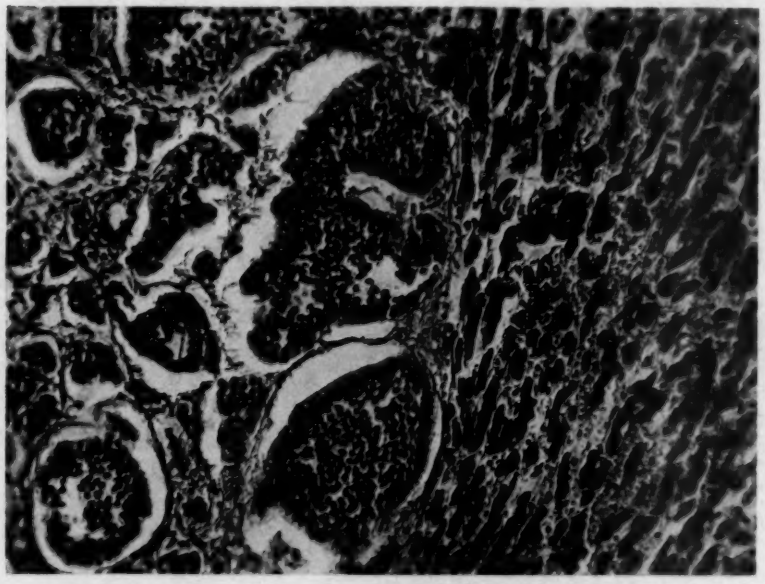

Fig. 2 (case 1).—Metastasis of argentaffin tumor in the liver ; × 130.

At autopsy, a constriction of the ileum was found, narrowing the lumen to 4 mm. and extending 2 cm. along the course of the intestine. The lower end of the lesion was 3 cm. from the ileocecal valve. There was scarring and puckering in the mesentery here, kinking the intestine. On one side of the constriction, there was a pedunculated mass, firm, grayish brown and about 1 cm. in diameter. There was a similar mass in the mesenteric attachment of this part of the intestine.

Microscopic Examination.—The histologic appearance here was in all respects similar to that of the intestinal tumors in the preceding case. Fixation in Zenker's fluid was used.

CASE 3.—A woman, aged 60, was the source of the third specimen of argentaffin tumor.

CASE 4.—The tissues from this and from case 3 were received from outside as surgical specimens without history, except that they were removed at operation from patients with symptoms of intestinal obstruction. Both of these tumors,

on staining by Masson's method, showed the characteristic silver-reducing granules in a great majority of the cells. The morphologic characteristics of these tumors were similar to those of the other two tumors, the differences being minor only.

COMMENT

Of the various hypotheses as to the nature of these tumors, none seems to offer a satisfactory solution of the problem. Masson's work in tracing their origin to the argentaffin cells of the intestine invalidates other opinions, and resolves the entire problem into a question of the nature of these cells. Masson feels that they form collectively an endocrine organ of entodermic origin. He speaks of a "neurocrine" organ in which the normal argentaffin cells of the intestine pour their secretion on the nerve-endings of an autonomic nerve plexus, also of entodermic derivation, not demonstrable with the technical methods now available. This supposition is based on the fact that many argentaffin tumors, particularly those of the appendix, are intimately associated with neuromas. In one of Barth's cases there was an accompanying neuroma with which the argentaffin cells were in close association. He does not follow Masson in interpretation of this, but brings up the interesting possibility of an affinity between nervous tissue and that of epithelial tumors analogous to the affinity in von Recklinghausen's disease between nervous and connective tissue. The cases investigated in this laboratory were purely epithelial.

Kull expressed the belief that their secretion is poured into the blood capillaries, and Parat said that he was in general accord with this opinion.

I believe that the evidence in favor of these propositions is not sufficient to justify the acceptance of either. The intestinal cells in question contain chromaffin granules as do the chromaffin cells of the suprarenal medulla; this, however, shows merely a chemical similarity, and is not conclusive proof of functional analogy. Even the chemical analogy is not complete, for the suprarenal granules are not stained with chrome salts after any fixation in which acetic acid is used, whereas the intestinal granules stain well after fixation with Bouin's fluid, which includes 5 per cent glacial acetic acid. Neither is there any physiologic evidence, for argentaffin tumors either are symptomless or give rise to symptoms only by causing intestinal obstruction, interference with the circulation or other result of position. In this they are unlike most endocrine tumors, e. g., those of the hypophysis, thyroid gland, suprarenal glands, gonads and some even of the islands of Langerhans.

Kulschitzky [7] felt that the granules in the cells that he described bore a definite relation to digestion and absorption in the intestine. After

7. Kulschitzky, N.: Zur Frage über den Bau des Darmkanals, Arch. f. mikr. Anat. **49**:7, 1897.

starvation of his experimental animals (dogs), he found that the granules in the cells were decreased in number; in animals on a plentiful diet that were killed after a few days, the granules were increased over the normal number. His observations have been declared incorrect by Kull, Suda and several others.

Cordier stated the belief that the cells have a definite exocrine function and pour their secretion into the intestinal lumen.

CONCLUSIONS

It is evident in reviewing the varying opinions concerning the nature of argentaffin tumors that an understanding of this question depends on further investigation of the chromo-argentaffin cells of the normal intestine. Until these are thoroughly understood one can say only that argentaffin tumors are similar in characteristics and especially in degree of malignancy to basal cell epitheliomas of the skin. Even this statement has its exceptions, for metastases do occur, though rarely.

SUMMARY

Four cases of argentaffin tumor of the small intestine (carcinoid) are reported, one with mesenteric and hepatic metastases. A brief review of opinions as to the nature of these tumors is made, and the conclusions drawn are (1) that the nature of the tumors depends on the nature of the chromo-argentaffin cells of the normal intestine, not yet understood, and (2) that until this point is decided, argentaffin tumors must be placed in the same category as basal cell epitheliomas of the skin, with reference to malignancy and general characteristics.

EXPERIMENTAL SUBACUTE AMYLOID NEPHROSIS IN RABBITS*

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In the course of studies on chronic metal poisoning, I noted a curious and interesting lesion in the kidneys of rabbits receiving manganese chloride subcutaneously. The lesion consisted of a marked subacute nephrosis involving the tubules and glomeruli, accompanied by the deposition of an amyloid-like substance in the glomerular tufts and about the tubular capillaries.

To my knowledge such an observation has not been recorded as a result of metal poisoning, and it was thought to be of sufficient interest to be made the subject of a report.

Manganese poisoning in man produces a peculiar combination of degenerative lesions in the basal ganglions of the brain and cirrhosis of the liver, a condition not unlike that of hepatolenticular degeneration as described by Wilson [1] and others. Mainly because of this fact, much experimental work has been done with manganese.

It is of interest to recall that Mella,[2] by injecting manganese into monkeys, reproduced the lesions described as characteristic of manganese poisoning in man. Later Findlay [3] reported cirrhotic changes in the livers of rabbits, guinea-pigs and rats poisoned with manganese.

Hurst and Hurst [4] summarized the literature and verified Findlay's observations, producing fibrous changes in the livers of guinea-pigs and rabbits with subcutaneous injections of manganese chloride. However, they were unable to demonstrate changes in the central nervous systems of their animals.

Primarily, my work was undertaken with the idea of disproving or substantiating the possibility that chronic manganese poisoning in rabbits gives rise to a similar deposition of pigment in the livers, as was found by Hall and myself [5] in our experiments confirmatory of Mallory's work with copper.

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* Submitted for publication, June 16, 1930.

* From the Department of Pathology, Stanford University Medical School.

1. Wilson: Brain **34**:290, 1911.

2. Mella: Experimental Production of Basal Ganglion Symptomatology in Macacus Rhesus, Arch. Neurol. & Psychiat. **11**:405, 1924.

3. Findlay: Brit. J. Exper. Path. **5**:92, 1924.

4. Hurst and Hurst: J. Path. & Bact. **31**:303, 1928.

5. Hall and Butt: Experimental Pigment Cirrhosis Due to Copper Poisoning; Its Relation to Hemochromatosis, Arch. Path. **6**:1, 1928.

It is perhaps not irrelevant to point out that this investigation acts as a control on our former work with copper. Furthermore, it must be stated that in our studies with both copper and manganese, carrots were purposely omitted from the diet.

Much work has been done on the production of amyloid disease. No attempt will be made to summarize the voluminous literature on the subject. In passing, mention will be made of the more recent work of Kuczynski,[6] further elaborated by Smetana,[7] in regard to the production of amyloid disease in mice by injections of nutrose. More recently Yokoi[8] reported that with intravenous injections of defibrinated blood, serum, or natrium silicate, amyloid disease may be produced in these animals. Letterer[9] has made a comprehensive study of the experimental development of amyloid in mice, producing the disease with injections of proteins, colloidal sulphur or colloidal selenium.

EXPERIMENTAL PROCEDURE

Young, healthy rabbits of about the same age, 6 months, were selected for the experiment. The animals were kept in separate cages and maintained on a diet consisting of barley, alfalfa and lettuce or cabbage leaves.

At irregular intervals, twenty-four hour samples of urine were collected, and quantitative tests for albumin and examinations of sediment were made. The method of Shevky and Stafford[10] was employed for the quantitative estimation of albumin.

Subcutaneous and intravenous injections were made, aseptic precautions and sterile solutions being used.

Autopsy was performed on the animals within twenty-four hours after death. Sections of the kidneys, liver, heart and adrenal glands were placed in Orth's solution and in 65 per cent alcohol. The tissues fixed in Orth's solution were examined for fatty changes. The alcohol-fixed tissues were embedded in paraffin, sectioned and stained with hematoxylin and eosin or van Gieson's stains. Methyl violet and iodine were used to identify the amyloid.

RABBITS RECEIVING SUBCUTANEOUS INJECTIONS OF MANGANESE CHLORIDE

Ten rabbits were given injections of manganese chloride two or three times a week. See table 1 for the details.

Rabbits 1, 2 and 3 were killed by an overdose of manganese after having received injections of smaller doses over a period of twelve weeks. Rabbit 4 had an injection of the same dose, but subsequently

6. Kuczynski: Virchows Arch. f. path. Anat. **239**:185, 1922.
7. Smetana: Bull. Johns Hopkins Hosp. **37**:408, 1925.
8. Yokoi: Tr. Jap. Path. Soc. **19**:343, 1929.
9. Letterer: Beitr. z. path. Anat. u. z. allg. Path. **75**:487, 1926.
10. Shevky and Stafford: Clinical Method for Estimation of Protein in Urine and Other Body Fluids, Arch. Int. Med. **32**:222, 1923.

recovered. Gross examination of the organs revealed no abnormalities, except intense congestion of the lungs and mottling of the livers. Histologic examination of the tissues showed numerous small areas of necrosis in the livers, extensive hemorrhage and edema in the lungs

TABLE 1.—*Rabbits Receiving Subcutaneous Injections of Manganese Chloride*

Rabbit	Duration of Experiment, Wk.	Number of Injections	Total $MnCl_2$ Received, Gm.	Albumin in Urine, Mg. per 24 Hr. Specimen at Termination of Experiment	Lesions of Kidney	Amyloid in Kidney	Lesions of Other Organs	Amyloid in Other Organs
1	12	27	0.062	.....	Cloudy swelling, tubular necrosis	None	Liver: areas of necrosis, small amount of pigment	None
2	12	27	0.062	.....	Cloudy swelling, tubular necrosis	None	Liver: areas of necrosis, small amount of pigment	None
3	12	27	0.062	.....	Cloudy swelling, tubular necrosis	None	Liver: areas of necrosis, small amount of pigment	None
4	34	80	0.482	1010.0	Marked tubular and glomerular involvement, moderate interstitial scarring	+++	Liver: areas of necrosis, slight increase of periportal fibrous tissue, terminal pericarditis	None
5	39	75	0.500	1094.0	Marked tubular and glomerular involvement, moderate interstitial scarring	+++	Spleen: pigment Liver: small amount of pigment	None
6	48	107	0.876	86.0	Moderate tubular and glomerular involvement	++	Lung: bronchopneumonia Liver: moderate increase in periportal fibrous tissue Spleen: pigment	None
7	48	108	0.929	110.0	Moderate tubular and glomerular involvement	++	Lung: bronchopneumonia Spleen: pigment	None
8	17(F) 8(S)	(17)F 13 S	1.050 0.154	1000.0	Marked tubular and glomerular involvement, moderate interstitial scarring	+++	Lung: hemorrhage Heart: interstitial scarring	Spleen
9	46	78	0.9768	120.9	Moderate tubular and glomerular involvement	++	Lung: hemorrhage	None
10	43	54	0.9954	1242.0	Marked tubular and glomerular involvement, moderate interstitial scarring	+++	Lung: hemorrhage	None

and congestion, cloudy swelling, epithelial necrosis and casts in the tubules of the kidneys. In all three animals, there were small amounts of finely granular, brown pigment in the liver cells about the periphery of the lobules. This pigment neither stained with fuchsin nor gave a positive reaction in the test for iron.

The remaining seven rabbits of this group received injections over a period of from twenty-five to forty-eight weeks.

It is interesting to note that when the kidneys were severely damaged the daily output of albumin in the urine was high, in some cases amounting to over 1 Gm. a day. The normal excretion of albumin in the urine of rabbits varies from 20 to 80 mg. per twenty-four hours.

Rabbit 4 died in uremic coma. The blood urea just prior to the death of the animal was 258 mg. per hundred cubic centimeters of blood.

A general description of the gross and microscopic appearances of the organs of these rabbits will suffice, as the changes were identical, except for quantitative and minor differences. Of all the organs, the kidneys presented the most constant and severe lesions. The kidneys were pale and swollen, and when tested with iodine the glomeruli stood

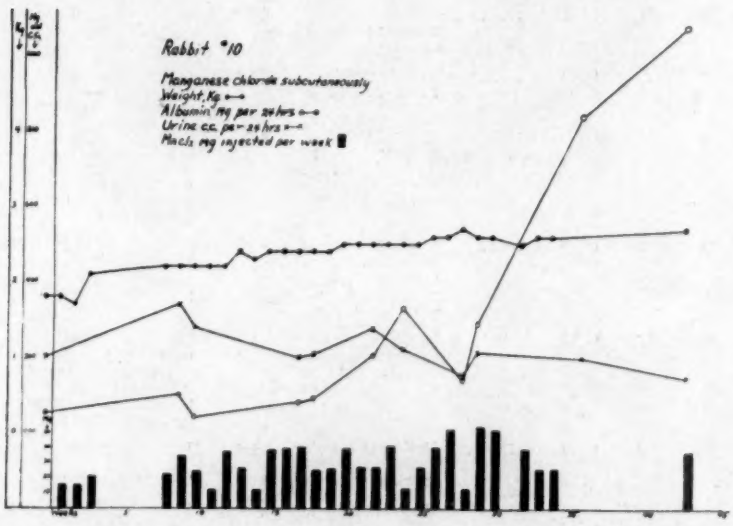

Fig. 1 (rabbit 10).—Weekly record of the weights and amounts of manganese chloride injected subcutaneously and the quantities of urine and albumin excreted in twenty-four hour periods.

out as small brown dots. Microscopically there were extreme changes in the tubules, particularly involving the first, second and third parts of the proximal convoluted portions and the medullary loops. These changes consisted of marked fatty degeneration and necrosis of the epithelial cells, accompanied by evidences of regeneration. Many of the proximal convoluted tubules were dilated to five and six times their normal size; some were completely denuded of epithelium, while others were irregularly lined with large, clear, oval cells, having pale-staining nuclei, or flat, fusiform epithelial cells with large nuclei. In a few places, the epithelial cells formed small masses projecting into the lumina. Some of the tubules contained casts; others, granular material.

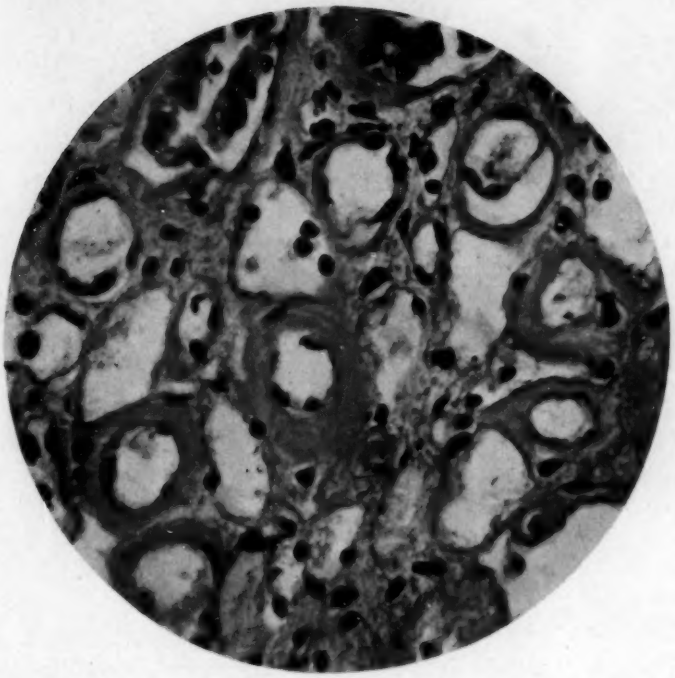

Fig. 2.—High power photomicrograph of kidney of rabbit 10, showing the amyloid infiltration about the tubular capillaries and the broad inner zone of the medulla.

Fig. 3 (rabbit 8).—A glomerulus infiltrated with amyloid, seen with high power objective.

The changes in the distal parts of the loops of Henle and in the distal convoluted and collecting tubules were negligible. There was a definite but moderate proliferation of interstitial fibrous tissue more marked in the kidneys having markedly dilated tubules. This was not accompanied by any signs of inflammatory reaction.

The glomerular changes were extremely interesting. Many of the capsular spaces were filled with granular material and in some places contained small amounts of blood. Throughout, the glomerular tufts were infiltrated with varying amounts of an amyloid-like substance that in places completely obliterated the glomeruli. This same substance was found about the tubular capillaries and was more in evidence about the capillaries of the medulla. This amyloid-like substance stained red with methyl violet and brown with iodine. The iodine brown color changed to a greenish blue when treated with sulphuric acid. Except for a moderate increase of perivascular fibrous tissue, the arteries were normal.

The renal changes in rabbits 6, 7 and 9 were less severe than those in rabbits 4, 5, 8 and 10, but in all there were varying amounts of amyloid.

The amyloid degeneration was limited entirely to the kidneys, except in rabbit 8, in which the spleen, in addition to the kidneys, was found to contain amyloid. This rabbit, by the way, was fed manganese chloride daily for a period of seventeen weeks, receiving a total of 1.05 Gm., and then later was given subcutaneous injections, receiving 0.154 Gm. of the metallic salt over a period of eight weeks.

The changes noted in the livers of these animals were variable and of little consequence. Grossly, the livers were normal, except for intense congestion. In three rabbits there were a few small areas of necrosis and slight increases of periportal fibrous tissue. In two rabbits there were slight amounts of finely granular, brown pigment in the liver cells about the peripheries of the lobules.

Only one rabbit of this group presented subcutaneous abscesses as a result of the injections. The sites of injections in the remainder of the rabbits presented no evidence of sloughing or of abscess formation.

RABBITS RECEIVING INTRAVENOUS INJECTIONS OF MANGANESE CHLORIDE

Three rabbits were given intravenous injections of manganese chloride (table 2). The kidneys of rabbit 11 were slightly swollen and microscopically presented lesions as follows: The tubular epithelium was swollen, granular and necrotic in places. The tubules and glomerular spaces were filled with granular material. Some of the

glomerular tufts appeared shrunken; others were swollen, vacuolated and markedly congested. In a few places, the glomerular tufts were replaced by a mesh of fibrin in which there were red blood cells. About a few of the capillaries of the medulla of the kidney there were small amounts of amyloid. Lesions in the other organs consisted of areas of necrosis in the liver and hemorrhages in the lungs. The spleen was found to contain much iron-bearing pigment. In the liver there were small deposits of pigment confined to the liver cells about the lobular peripheries.

The remaining two rabbits received injections of smaller doses of the metal over a longer period of time. One rabbit showed large subcutaneous abscesses and was killed at the end of the thirty-fourth week.

TABLE 2.—*Rabbits Receiving Intravenous Injections of Manganese Chloride*

Rabbit	Duration of Experiment, Wk.	Number of Injections	Total $MnCl_2$ Received, Mg.	Albumin in Urine, Mg. per 24 Hr. at Termination of Experiment	Lesions of Kidney	Amyloid in Kidney	Lesions of Other Organs
11	10	18	0.242	1101.6	Marked tubular and glomerular necrosis	+	Spleen: pigment Liver: necrosis, small amount of pigment
12	42	70	0.5104	130.4	Marked cloudy swelling; otherwise normal	None	Spleen: pigment Liver: moderate amount of pigment
13	34	58	0.2626	156.6	Moderate cloudy swelling; otherwise normal	None	Spleen: pigment Liver: small amount of brown granular pigment

The other animal was killed at the end of the forty-second week. Except for a moderate parenchymatous degeneration, the kidneys of both animals were normal. No amyloid was demonstrated. The livers and spleens contained moderate amounts of hematogenous pigment.

RABBITS FED WITH MANGANESE CHLORIDE

Five rabbits were given manganese chloride, daily, in their food for from eleven to forty-one weeks (table 3). The end-results were negative, and in none of the rabbits of this group were there evidences of damage of the kidneys or liver attributable to the action of the metal. Two of the animals (14 and 17) developed bronchopneumonia, accompanied by abscess formation. There were areas of necrosis in the liver of rabbit 14, and it seemed most likely that this lesion resulted from the severe pneumonic infection. There was a small amount of finely granular, brown pigment in the liver of rabbit 18, a lesion not demonstrated in the remaining four animals.

RABBITS RECEIVING SUBCUTANEOUS INJECTIONS OF (1) ZINC LACTATE, (2) MERCURIC CYANIDE

Two rabbits received injections of zinc lactate for thirty-eight weeks, each receiving a total of 1.65 mg. (table 4). Both rabbits developed large areas of sloughing at the sites of injection. Grossly and microscopically, the organs were normal.

TABLE 3.—*Rabbits Fed Manganese Chloride*

Rabbit	Duration of Experiment, Wk.	Number of Feedings	Total $MnCl_2$ Received, Gm.	Albumin in Urine, Mg. per 24 Hr. at Termination of Experiment	Lesions of Kidney	Amyloid in Kidneys	Lesions of Other Organs
14	12	62	1.05	Test not done	None	None	Liver: necrosis
15	16	62	1.05	Test not done	None	None	Spleen: pigment
16	11	66	3.12	26.1	None	None	Liver: fatty infiltration
17	21	126	9.72	50.4	None	None	Liver: fatty infiltration Lung: bronchopneumonia
18	41	312	46.92	64.8	None	None	Liver: small amount pigment, fatty infiltration

TABLE 4.—*Rabbits Receiving Subcutaneous Injections of (1) Zinc Lactate and (2) Mercuric Cyanide*

Rabbit	Duration of Experiment, Wk.	Number of Injections	Total Metal Received	Albumin in Urine, Mg. per 24 Hr. at Termination of Experiment	Lesions of Kidney	Amyloid in Kidneys	Lesions of Other Organs
45	38	33	Zinc lactate, 1.65 mg.	46.0	Cloudy swelling	None	None
46	38	33	Zinc lactate, 1.65 mg.	57.2	Cloudy swelling, small amount tubular necrosis	None	None
27	44	56	Mercuric cyanide, 0.341 Gm.	594.0	Marked tubular necrosis, glomerular changes, interstitial fibrosis	None	Liver: small areas of necros.s
28	44	56	Mercuric cyanide, 0.278 Gm.	518.4	Same as in 27, except less marked	None	Spleen: pigment Liver: cloudy swelling

The remaining two rabbits received respectively, 0.341 and 0.278 Gm. of mercuric cyanide, over a period of fifty-six weeks. Both rabbits developed subacute lesions of the kidney, typical of the usual observations in mercury poisoning.

No amyloid was found in the organs of the four rabbits.

CONTROLS

Suffice it to say that an adequate number of control rabbits, twelve, maintained on the diet given above presented no gross or microscopic lesions.

COMMENT

Local amyloid degeneration in kidneys of rabbits severely damaged by subcutaneous injections of manganese chloride is a constant observation, and moreover properly regulated doses of the same metal given intravenously give rise to the same lesion.

The production of the lesion of the kidney depends on giving manganese chloride over a long period of time, thus making it necessary to regulate the dose to the individual tolerance of the animal. This may be done by following the daily weights and the quantitative estimations of albumin in the urine.

At present, I am repeating and varying the experimental procedure with the hope of finding an explanation of the formation of amyloid in this lesion. I believe, however, that capillary damage, followed by the exudation and jelling of protein substance from the blood into the pericapillary spaces, is the most likely explanation. Nevertheless, I am mindful of the fact that the production of this amyloid substance may be a local phenomenon.

Local suppuration at the sites of injection of the metal may be definitely excluded as the cause of the amyloid degeneration, as only one rabbit of the group receiving subcutaneous injections developed abscesses, and the kidneys of this rabbit contained less amyloid than the kidneys of the remainder of the rabbits. This possibility was further controlled by subcutaneous injections of zinc lactate and mercury cyanide into rabbits, the former producing large areas of sloughing subcutaneously, and the latter giving rise to little or no effect locally but causing severe renal tubular damage typical of mercury poisoning, but in neither case resulting in local amyloid degeneration of the kidneys.

I am unable to explain why the damage of the liver that I observed was not so extensive as that which other authors have reported. It may be that higher doses of manganese chloride than I have employed are necessary to cause such damage.

Hurst and Hurst [4] reported the finding of pigment in the livers of their rabbits given manganese and concluded: "The pigment in manganese poisoning is like that in phenylhydrazine poisoning, a product of blood destruction, and manganese has in addition to the effect on the liver some slight hemolytic action; the pigment is not hemofuchsin." It will be seen in my tables that some pigment was demonstrated in the livers of the rabbits, a most constant observation in rabbits into which manganese chloride had been intravenously injected. The pigment was finely granular and did not stain with fuchsin or by Perl's prussian blue method. In fact, it does not resemble the type of pigmentation that copper produces, in quantity or in quality.

I was unable after thorough search to find pigment in the livers of the control rabbits. The question of the pigment will be considered in a later paper.

CONCLUSIONS

A method has been found to produce amyloid nephrosis in rabbits. The production of the lesion depends on the regulation of the doses of manganese chloride given subcutaneously so as to permit chronic poisoning. The amyloid degeneration is usually limited to the kidneys, except occasionally when the spleen in addition to the kidneys may be involved. The identification of this amyloid-like substance as amyloid is based on its reaction with the stains that are considered specific for amyloid, i. e., methyl violet and iodine.

STUDIES ON THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS: II*

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AND
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In a previous communication [1] it was reported that staphylococcus bacteremia of rabbits led to endocarditis in a high percentage of the animals if, previous to the infection, the animals had received ten intravenous injections of sodium caseinate. Since the control animals, even when given as many as thirty daily injections of casein, failed to show lesions of the endocardium, we drew the inference that our results were due to an altered capacity of the endocardium to react toward bacteria.

Other investigators of the pathogenesis of endocarditis, for example, Dietrich [2] and Freifeld,[3] concluded from their experiments that endocardial localization of bacteria presupposes an "activation" of the endothelium, i. e., its transformation into endothelial phagocytes.

In order to submit the aforementioned theory to an experimental test, we observed the reaction of the endocardium of rabbits that had received injections of casein toward india ink and carmine. The technical details of the experiment are recorded in the accompanying table.

The histologic observations were identical in all animals that received injections whether of india ink or carmine suspended in distilled water. Neither the controls nor the animals previously treated with casein showed phagocytosis of carbon or carmine particles by the endothelial coat of the endocardium. All animals that received injections of lithium carmine showed a finely granular deposit of carmine in the histiocytes of the endocardium. The amount and the distribution of the carmine deposits in the controls did not differ from those in the animals treated with casein. No karyorrhexis of either the endothelium or the histiocytes of the heart valves and no other regressive changes of the endocardium were found. Numerous sections of the myocardium, liver, spleen and bone-marrow failed to reveal any regressive or progressive

* Submitted for publication, June 12, 1930.

* From the Institute of Pathology of the Western Pennsylvania Hospital; Dr. Ralph R. Mellon, director.

1. Semsroth, K., and Koch, R.: Studies on the Pathogenesis of Bacterial Endocarditis, Arch. Path. **8**:921, 1929.

2. Dietrich, A.: Deutsche Gesellsch. f. inn. Med. **27**:188, 1925.

3. Freifeld, H.: Klin. Wchnschr. **7**:1645, 1928.

changes. In particular, there was no focal proliferation of the Kupffer cells of the liver and no amyloidosis such as that reported by Kuczynski [4] as a sequel of repeated intramuscular injections of casein in mice. The theory of endothelial activation in the sense of a transformation of the endothelium into phagocytes can therefore be dismissed as contrary to experimental observations. The altered capacity of the endocardium to react toward bacteria has to be explained in some other way.

Experiment to Determine the Effect of Injections of Casein on the Function of the Reticulo-Endothelial System

Days of Injection	Intravenous Injections Given Various Groups of Rabbits					
	1	1a (Controls)	2	2a (Controls)	3	3a (Controls)
1st-10th day	2% sodium-caseinate, 1 cc. increasing to 5 cc.	.....	2% sodium-caseinate, 1 cc. increasing to 5 cc.	.....	2% sodium-caseinate, 1 cc. increasing to 5 cc.	.....
11th day						
9 a.m.	5 cc. india ink (a 1:3 dilution in distilled water)	5 cc. india ink (a 1:3 dilution in distilled water)	4 cc. carmine (5% suspension in distilled water)	4 cc. carmine (5% suspension in distilled water)	5 cc. lithium carmine (5% carmine dissolved in saturated lithium carbonate)	5 cc. lithium carmine (5% carmine dissolved in saturated lithium carbonate)
4 p.m.	5 cc. india ink (a 1:3 dilution in distilled water)	5 cc. india ink (a 1:3 dilution in distilled water)	4 cc. carmine (5% suspension in distilled water)	4 cc. carmine (5% suspension in distilled water)	5 cc. lithium carmine (5% carmine dissolved in saturated lithium carbonate)	5 cc. lithium carmine (5% carmine dissolved in saturated lithium carbonate)
12th day						
9 a.m.	5 cc. india ink (a 1:3 dilution in distilled water)	5 cc. india ink (a 1:3 dilution in distilled water)	4 cc. carmine (5% suspension in distilled water)	4 cc. carmine (5% suspension in distilled water)	5 cc. lithium carmine (5% carmine dissolved in saturated lithium carbonate)	5 cc. lithium carmine (5% carmine dissolved in saturated lithium carbonate)
11 a.m.	All animals were killed. Autopsies were performed on all, and sections of heart, liver, spleen, bone-marrow and kidneys were prepared					

THE EFFECT OF INTRAVENOUS INJECTIONS OF CASEIN OR OF KILLED STREPTOCOCCI ON THE FUNCTIONAL STATE OF THE RETICULO-ENDOTHELIAL SYSTEM

In a study of the behavior of the vitally stained host against infections, Silberberg [5] produced endocarditis regularly when he infected rabbits subsequent to a series of injections of lithium carmine. Since lithium carmine is deposited in the cells of the reticulo-endothelial system, the assumption that changes in the function of the reticulo-endothelial system are involved in the pathogenesis of endocarditis was considered worthy of

4. Kuczynski, M. H.: Virchows Arch. f. path. Anat. **239**:185, 1922.
5. Silberberg, M.: Virchows Arch. f. path. Anat. **267**:483, 1928.

experimental study. The method that we used for demonstrating such a relationship differed from the method that Silberberg used and that is generally applied for the study of the reticulo-endothelial system. Commonly, dyes are used as a means for influencing the function of the reticulo-endothelial system, often with the object of a so-called blockade in mind. The limitations of such a procedure are evident and have been pointed out repeatedly. The more promising way seemed to be to use the dyes as indicators of the function of the reticulo-endothelial cells, after the animals had received parenteral applications of casein.

Another series of animals was given injections according to the technic given in the table. The animals were killed two hours after the last injection, autopsies performed and sections of spleen, liver and bone marrow prepared.

The histologic observations were identical in all animals receiving injections of india ink or carmine suspended in distilled water. The storage of carbon or carmine particles by the organs of the reticulo-endothelial system—liver, spleen and bone marrow—in the animals treated with casein was not found to differ from that in the controls. Rabbits treated with casein, however, and receiving injections of lithium carmine showed only traces of granular carmine, while normal control rabbits showed an ample deposit of finely granular carmine.

If this change in the function of the reticulo-endothelial cells, indicated by the absence of carmine deposits, is associated with the pathogenesis of endocarditis and is not due to a specific action of the casein, any procedure that leads to an experimental endocarditis should present this change under controlled conditions. Freifeld [3] showed that staphylococcus bacteremia of rabbits leads to endocarditis if the animals have been subjected to six daily injections of killed streptococci previous to the infection.

For an experimental test of this assumption, the technic recorded in the table was modified by replacing the injections of casein with six daily injections of killed streptococci. The dyes were injected, as in the previous experiment, on the seventh and eighth days. All animals were killed two hours after the last injection of dye, autopsies performed and sections prepared. The results were identical with those of the previous experiments. The main features are summarized schematically in figure 1.

Further information about this change in the function of the reticulo-endothelial cells was gained by a study of animals killed at varying periods after the last injection of dye.

In normal rabbits, the amount of lithium carmine deposited increased up to two hours and then persisted in this quantity for at least a week. In rabbits that received ten daily injections of sodium caseinate and

then three injections of lithium carmine, examination after one-half hour revealed absence of the dye; after one hour, about half of the amount of carmine present in the cells of a normal animal could be seen; after two hours, the dye had disappeared.

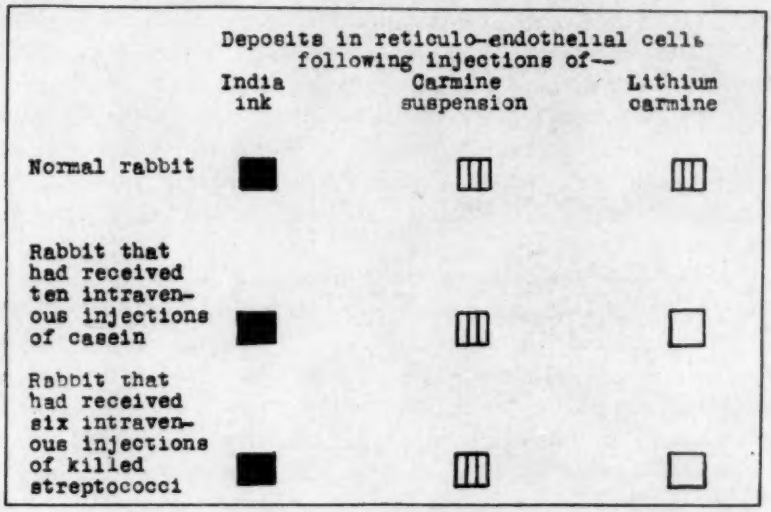
Deposits in reticulo-endothelial cells following injections of—
India ink
Carmine suspension
Lithium carmine
Normal rabbit
Rabbit that had received ten intravenous injections of casein
Rabbit that had received six intravenous injections of killed streptococci

Fig. 1.—The effect of a series of injections of casein or of killed streptococci on the reticulo-endothelial system of rabbits, as shown by deposition of subsequently injected india ink, carmine suspension or lithium carmine in the reticulo-endothelial cells. The solid square represents carbon; the barred square, carmine, and the blank square, a reticulo-endothelial system free from deposits of dye. Each animal was killed two hours after the last injection of dye substance.

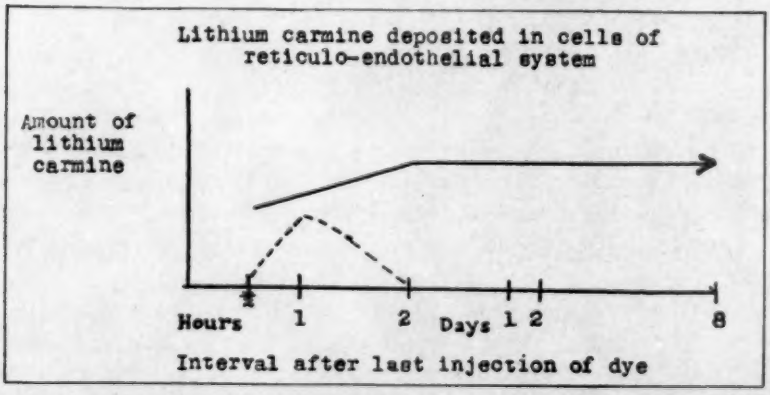

Fig. 2.—The deposit of lithium carmine in the cells of the reticulo-endothelial system of a rabbit that had received ten intravenous injections of casein. The solid line represents the deposit in a normal rabbit (control) and the dotted line that in the rabbit treated with casein.

Whether this change in the function of the reticulo-endothelial cells indicated by the variations of their behavior toward lithium carmine is primarily due to a metabolic or to a secretory disturbance of the cells themselves or is secondary to excretory disturbance remains a matter for further study. Repeated injections of foreign proteins led, in the experience of Haendel and Malet,[6] to an increased ability of the reticulo-endothelial system to store india ink. While these authors regarded their results as proof of increased function, our own experience shows that such a conclusion is misleading. When a solution of lithium carmine is used as an indicator—instead of a suspension—repeated intravenous injections of a foreign protein are found to lead to a function that could be termed "decreased," if the amount of dye deposited is taken as a criterion, or "increased," if the rate of disappearance of the dye is made the sole point of interest. This matter is then a relative one, unless other supporting criteria are invoked that will prove physiologically decisive.

EXPERIMENTAL TOXIC ENDOCARDITIS AND MYOCARDITIS

A deleterious effect of bacterial toxic products on the heart valves preceding the endocardial localization of bacteria was considered important by Ribbert.[7] Wadsworth,[8] studying endocarditis in pneumococcus-immunized horses, was led to conclude that "bacterial poisons produce the predisposing injury." Experimental proof of such a predisposing rôle of bacterial toxic products is, however, extremely scanty.

While the production of endocardial lesions by means of a toxin in a few experimental animals was reported by de Veechi,[9] these processes were not accepted by Ribbert as truly inflammatory. Experimental investigations into the action of bacterial toxins must take into consideration absorption and fixation of these toxins in various tissues. In this process, the reticulo-endothelial system plays a prominent rôle, as demonstrated by recent investigations.

It was shown previously that intravenous injections of casein or of streptococcic vaccine led to a definite functional change of the reticulo-endothelial system, on the one hand, and to a predisposition of the animal to endocardial localization of bacteria, on the other. We were led to infer that a relationship between this functional change of the reticulo-endothelial system and the endocardial localization of bacteria

6. Haendel, M., and Malet, J.: Deutsche med. Wchnschr. **55**:617, 1929.

7. Ribbert, H., in Henke and Lubarsch: Handbuch der speciellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, pp. 203 and 209.

8. Wadsworth, A. B.: J. M. Research **39**:279, 1918-1919.

9. de Vecchi, quoted by Ribbert (footnote 7, p. 209).

may exist through an increased deleterious effect of bacterial toxins on the heart. The validity of this inference was confirmed in the following experiments:

Experiment 1.—In a first series, four rabbits received ten intravenous injections of a 2 per cent solution of casein. They were subsequently given intravenously from 0.0002 to 0.1 cc. of a diphtheria toxin. Four control animals received like doses of the same diphtheria toxin. Autopsies were done on the first, second or fifth day after the injection of the toxin. Serial sections of the heart were prepared in all cases.

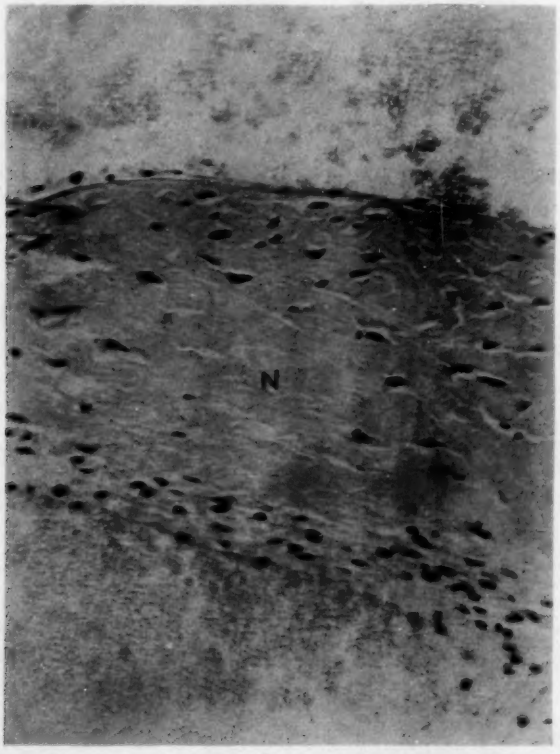

Fig. 3.—An area (*N*) of homogenization and necrobiosis in a heart valve of a rabbit that had received ten intravenous injections of casein and then an intravenous injection of 1 cc. of a 1:1,000 dilution of diphtheria toxin.

Histologic Observations: In the control animals, a few small areas of necrobiosis were found within the valvular substance. No further valvular lesion and no myocarditis was noticed. In the animals that had been prepared with injections of casein, areas of hyaline transformation of the valvular substance with scarcity of nuclei were observed (fig. 3). At numerous places, focal accumulations of large, oval—in many instances, bizarre-shaped—nuclei were seen. Karyorrhexis and formation of multinuclear cells were present (fig. 4). In some instances, a valve showed a definite polymorphonuclear leukocytic infiltration, an exudative valvulitis (fig. 5).

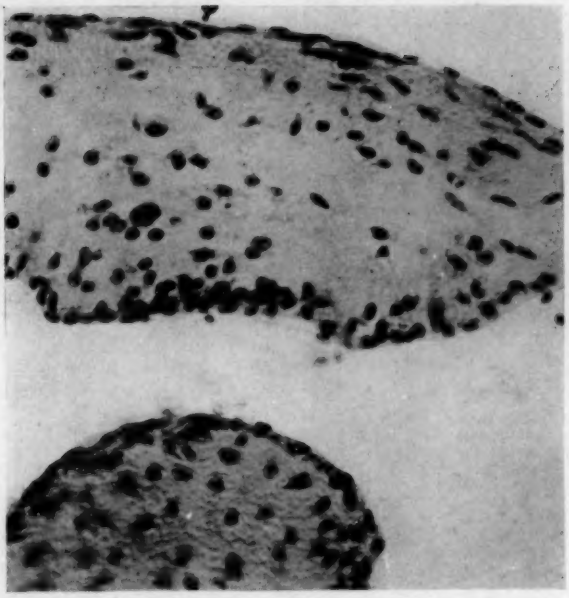

Fig. 4.—A focal proliferative reaction of a heart valve of a rabbit that had received ten intravenous injections of casein and then an intravenous injection of 1 cc. of a 1:10 dilution of diphtheria toxin.

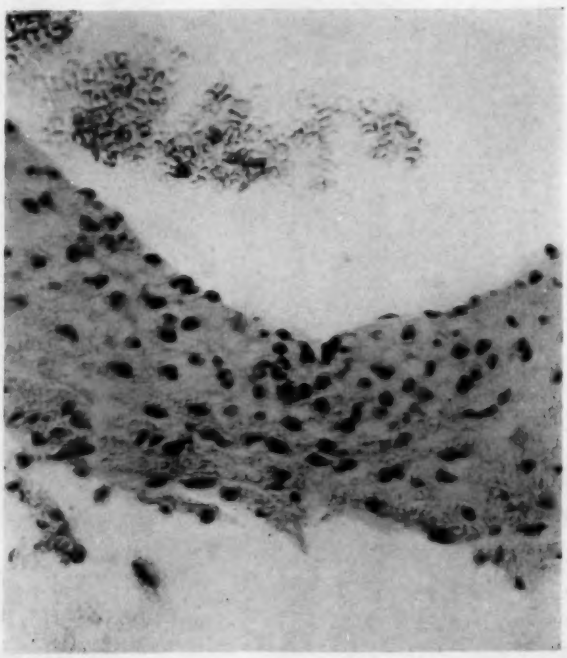

Fig. 5.—Acute exudative valvulitis in a rabbit that had received ten intravenous injections of casein and then an intravenous injection of 1 cc. of a 1:10 dilution of diphtheria toxin.

In all four of the animals treated with casein, the myocardium showed focal interstitial inflammatory lesions. They were characterized by accumulations of lymphocytes with a few eosinophil leukocytes and proliferation of large mononuclear elements, presumably histiocytes; i. e., they bore a close analogy to the focal myocarditis of human endocarditis.

Experiment 2.—In a second series, two rabbits received ten intravenous injections of 2 per cent solution of casein and two more rabbits six intravenous injections of a streptococcic vaccine. All four animals were subsequently given intravenous doses of killed typhoid bacilli, starting with 0.25 cc. and increasing by 0.25 cc. with each injection. They were killed seven days later.

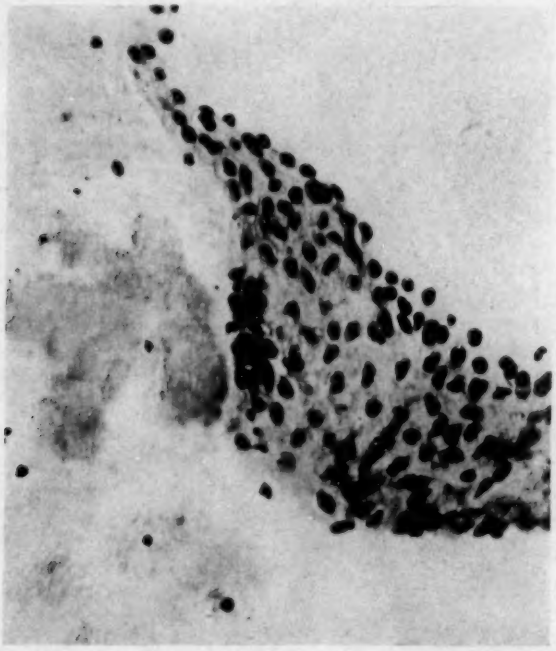

Fig. 6.—A hyaline thrombus over an area of advanced karyorrhexis and accumulation of finely granular chromatin (vaccine?) in a heart valve of a rabbit that had received ten intravenous injections of casein and then four intravenous injections of typhoid vaccine.

Four control animals received the same doses of typhoid vaccine without preceding injections of casein or streptococcic vaccine. They were killed seven days later. Serial sections of the heart were prepared in all cases.

Histologic Observations: Moderate hemorrhages into the heart valves and slight valvular edema were found in the controls, which had been treated with typhoid vaccine only. There was no further lesion of the heart valves. No myocardial change was noticed. Valvular hemorrhage and edema were present in the animals previously treated with casein or streptococcic vaccine, as in the controls. In addition, however, the valves of all these animals showed focal or more diffuse accumulations of large, oval, frequently bizarre-shaped nuclei with karyorrhexis in many instances (fig. 6). At a few places, masses of finely granular

chromatin were found within the superficial, broken-down valvular substance, covered by a "hyaline" thrombus. In one instance, the endocardial coat of a papillary muscle showed a definite inflammatory exudative process.

COMMENT

Two hypotheses have been advanced in explanation of the pathogenesis of endocarditis: (1) that of elective localization of certain bacterial strains and (2) that of endocarditis as an allergic phenomenon. Against the preponderant influence of the elective localization theory may be brought the evidence that the infection is not limited to one type of micro-organism, but is due to multiplicity of bacteria. The allergic theory offers a reasonable explanation of the divergent bacteriologic observations. The experimental investigations of a number of authors (Dietrich, Freifeld, Semsroth and Koch) have led to the conclusion that endocardial localization of bacteria presupposes a change in the reactivity of the host. As to the nature of this reactive change, considerable difference of opinion prevails.

A sensitization or activation of the endocardium in the sense of a transformation of its endothelium into phagocytes was assumed to be the decisive factor by Dietrich. Experimental work by Pfuhl [10] and our own results fail to reveal any evidence of such a transformation.

In contrast with this theory of activation stands the conception that some form of damage to the heart valves precedes endocardial localization of bacteria (Ribbert,[7] Wadsworth [8]). Experimental evidence that mechanical injury to the heart valves enables bacteria to localize on them has been available for a considerable length of time. On the other hand, it has been shown that repeated injections of casein (or of killed streptococci or of lithium carmine) lead to localization of the bacteria on the endocardium in a high percentage of the experimental animals, but do not lead per se to a recognizable cellular damage of the endocardium. In the present paper, evidence has been brought forward that such measures (injections of casein, etc.) lead to a definite functional change of the reticulo-endothelial system. Furthermore, results have been obtained indicating that in the presence of the functional change the detoxifying effect of the reticulo-endothelial system is interfered with. Amounts of toxic bacterial products that in the normal animal fail to exert a deleterious effect on the heart valves lead to cellular damage and reaction. In the light of these results, the theory of a preceding cellular damage to the endocardium may well be upheld in a modified manner. Our observations suggest that a decisive factor in the pathogenesis of endocarditis is a disturbance of the detoxifying ability of the reticulo-endothelial system. In the presence

10. Pfuhl, W.: Ztschr. f. mikr. anat. Forsch. **17**:1, 1929.

of this disturbance, amounts of toxic bacterial products that are practically innocuous to the tissues of the normal animal lead to inflammatory lesions of the endocardium. This cellular damage in turn enables bacteria to localize on the endocardium.

SUMMARY

Repeated intravenous injections of casein or of killed streptococci do not lead to degenerative changes of the endocardium nor to a transformation of the endothelial coat of the endocardium into phagocytes. (There is no activation of the endothelium in the sense of Dietrich.)

Subsequent to repeated intravenous injections of casein or of killed streptococci, the phagocytosis of particles of colloidal dye by the reticuloendothelial system is not disturbed.

On the other hand, the response of the casein-sensitized reticuloendothelial system to a true solution of carmine (lithium carmine) is definite; the storage of this dye is markedly inhibited in the animals treated with casein in contrast with the control animals, which absorb it readily.

In the presence of this functional change, sublethal doses of diphtheria toxin and of killed typhoid bacilli exert an increased deleterious effect on the endocardium and myocardium. Such animals show inflammatory lesions of the endocardium and myocardium, while controls fail to show inflammatory lesions.

ENDOMETRIOMYOMA OF THE UMBILICUS*

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Tumors of the umbilicus are relatively infrequent. Among the most interesting are those containing tissue resembling endometrium. The resemblance is sufficiently close to entitle such tumors to the name of endometrioma. In view of the fact that some of these structures contain smooth muscle, the term endometriomyoma is more suitable. Adenomyoma may, strictly speaking, be a more correct term, since the proof that the glands and stroma are like endometrium in every essential or at least have the same immediate origin as endometrium is still wanting. Study of these tumors may throw some light on the origin of extra-uterine endometrial growths. Although it is by no means certain that all ectopic endometriomas have a common mode of origin, it seems fairly certain that the endometriomyomas of the umbilicus do not take origin from explanted, fully differentiated endometrium, a point which the instance reported here supports.

REPORT OF A CASE

A white girl, 18 years of age, noticed a small warty growth in the umbilicus six months before it was removed. This tumor was neither painful nor tender. A few days before the operation and ten days after menstruation, it oozed blood for the first time. The growth did not enlarge or become painful at the menstrual periods, but rather maintained a slow, steady increase in size until it was about 1 inch (2.5 cm.) in diameter. The menstrual history did not reveal any abnormalities. The tumor was excised by an elliptic incision, and was found to extend down to the peritoneum. The peritoneal cavity was opened, and the peritoneum lining the umbilical fossa was removed with the lumen. The abdominal cavity was not explored.

The specimen was a nodular, knobby growth, pouting out of the umbilical fossa and measuring 2.5 by 2 by 2 cm. The skin over the tumor followed the convolutions of the surface, dipping into the crevices. The cut surface was smooth and of a fibrous structure surrounded by fat. The center of the peritoneal surface was deeply dimpled. The tumor was not encapsulated, but was rather sharply limited. A few small cystic spaces could be discerned with the aid of a hand lens.

The sections revealed an adenomatous formation separated from the squamous epithelium by the corium and composed of rather densely packed smooth muscle fibers and cells and occasional strands of connective tissue. Glandular structures were scattered throughout the specimen, varying in size from small oval and round glands to larger cystic ones. These glandular structures were lined by a single layer of columnar, nonciliated cells, except in a few of the larger glands, in

* Submitted for publication, June 23, 1930.

* From the Laboratories of Mount Sinai Hospital.

which the cells were more cuboidal. Within several of the glands was hemorrhage, varying in amount from only a few to a considerable cluster of erythrocytes; there were also leukocytes and desquamated epithelial cells. Most of the glands were surrounded by a cellular stroma and occasionally there were small hemorrhagic extravasations. The stroma cells were elongated, spindle-shaped and closely packed. Occasional glands were found surrounded by more loosely arranged stroma, and here the cells assumed an oval shape. The stroma was not uniformly distributed around the glands, but was generally massed to one side (figs. 1 and 2).

Fig. 1.—Low power magnification showing general structure and relation of glands to skin.

The peritoneal surface of this tumor was of considerable importance and interest. The peritoneal cells were hyperplastic and almost columnar. These could be noted in the fold of peritoneum dipping into the dimple mentioned. Adjacent to the fold was an elongated glandular structure lined by low columnar epithelium, which by serial section could be traced to the peritoneum. This gland contained a few erythrocytes, but was not surrounded by endometrioid stroma. The lining epithelium resembled the hyperplastic peritoneal cells rather than the columnar cells of the glands first described.

One other glandular element was encountered. Two glandlike structures were found close to the peritoneal surface. Their lining epithelium was different from that of the other glands. They were lined by a single layer of large, mucus-secreting goblet cells. These glands were surrounded by a loose meshwork of connective tissue, and not by cellular, endometrioid stroma (fig. 3).

In some areas, a small amount of myxomatous-like material was found. This had the characteristic blurred, amorphous character of myxomatous degeneration,

Fig. 2.—High power magnification showing hemorrhage in glands and periglandular stroma.

and took a faint basophilic stain. These areas did not contain any cells, and were placed between the muscle and connective tissue fibers.

COMMENT

Whether or not one is justified in calling such tumors as this endometriomas may be disputed. At least, the resemblance of the glands

and surrounding stroma to endometrium is as close as that of the endometriomas in the broad ligament and in the pouch of Douglas and even of the adenomyomas of the uterus to true endometrium. So that until definite cytologic criteria are established for endometrium, the term is justified. The resemblance is further strengthened by the

Fig. 3.—Glands lined by goblet cells.

presence of hemorrhage. As the literature on this subject shows, many of the tumors bleed at the menstrual periods.

Naturally, the most interesting question concerns the origin of the tissues present in the tumor described. It seems unreasonable to attribute the tumor to transplanted bits of endometrium, carried either by the blood stream or by the lymphatics. If such a transportation occurred, it is difficult to explain how the tissue arrived at the umbilicus and grew in the abdominal wall without producing evidence of implantation else-

where. The implantation theory probably is most applicable to the endometriomas occurring in laparotomy scars, of which a goodly number have been reported. But here, too, this explanation is open to doubt, for it seems so unlikely that a needle passed through the outer layer of myometrium could pick up and transplant endometrial tissue, and this explanation certainly would not suffice for the occurrence of endometrioma following operations not involving the uterus.

It would seem that the specimen reported here offers evidence in favor of the local origin of the heterologous tissue. The direct continuity of peritoneum with one of the glands would point to a metaplasia of tissue of peritoneal origin. The finding of the mucus-secreting cells might indicate an origin from the omphalomesenteric duct, and the presence of smooth muscle fibers would lend support to this. However, whether one chooses to consider a direct origin from the remnant of the duct or from the peritoneum is of little moment, since their origin is a common one. Of course, one could on this basis attribute the origin of endometrial tissue in the umbilicus to a faulty differentiation of the entoderm, allowing that a few cells destined to become endometrium will be isolated at the umbilicus. This, however, becomes pure speculation.

Two elements in the case reported deserve further comment. The presence of the mucus-secreting cells may be considered accidental, or they may be considered as evidence of the local origin of the endometrioma. Roques [1] pointed out that portions of the vitelline duct occasionally persist at the umbilicus, but the epithelium does not possess the function of menstruation, nor are these portions surrounded by endometrial stroma. Since the two glands described were the only ones of this type found in a great many sections, it seems reasonable to consider them as remnants of the duct. From that point of view, they do not seem to be an integral part of the tumor, but rather were caught in the growth. Still, the possibility that these glands are the result of peritoneal metaplasia and have the same histogenesis as the endometrial tissue cannot be ignored, theoretically, especially if one remembers the multiple potencies of entoderm. It would be difficult to explain, however, why one group of cells went on to endometrial differentiation and another group differentiated into epithelium of the celomic type.

The smooth muscle forming an integral part of the tumor is also of importance. If endometrium could have been transplanted, it is hardly likely to have carried smooth muscle fibers with it, so that the local origin of the smooth muscle is probably beyond dispute. Meyer,

1. Roques, F.: Endometrial Tumors of the Umbilicus, Proc. Roy. Soc. Med. **21**:538, 1928.

Renesch, Nicholson [2] and others expressed the opinion that the smooth muscle fibers are derived from local tissues. In regions in which unstriped muscle is not found normally, its presence has been attributed to a metaplasia of the surrounding connective tissue. However, having once established an embryologic origin for the epithelial structures, it seems more rational to explain the presence of the smooth muscle on the same basis. It does not seem likely that one element of the tumor would have one origin and another element a different origin. Furthermore, there is no proof that explants of endometrium can stimulate smooth muscle metaplasia from connective tissue, or that the stroma cells of the endometrium can give rise to smooth muscle. Those who have explanted endometrium did not find smooth muscle cells in the explants, with one exception. Michon [3] transplanted minute pieces of endometrium into the ovary of the rabbit. There was hyperplasia of smooth muscle around the transplanted epithelium. It is possible that he introduced smooth muscle fibers along with the uterine mucosa. In experiments on tissue culture, with successful growth of endometrium, smooth muscle cells have not been found. Transplantation would account for the presence of smooth muscle in endometriomyomas in laparotomy scars, particularly after cesarean section, provided one considers the transplantation theory tenable, and it would have application in cases in which the tumor followed an operation during which the uterine cavity was opened.

Both the serosal theory and the theory of congenital misplacement seem to be applicable to the tumor reported here and likewise to the other instances reported in the literature.

Palmen [4] takes the stand that they probably originate from the embryonic umbilical epithelium, as yet undifferentiated, contrary to those cysts and fistulas arising from remains of the fully developed vitelline duct.

Weller,[5] at the meeting of the American Association of Pathologists and Bacteriologists in 1927, reported two cases of menstruating umbilical tumors. Smooth muscle was not found in either instance. He stated that the occurrence of these tumors at the umbilicus cannot be satisfactorily explained as being due to endometrial implantation or to lymphogenous or hematogenous metastases from proliferating endometrial

2. Nicholson, G. W.: Studies in Tumour Formation: Mixed Tumours, Guy's Hosp. Rep. **76**:188, 1926.

3. Michon, quoted by Jacobsen, V. C.: Ectopic Endometriosis, Arch. Path. **5**: 1054, 1928.

4. Palmen, A. J.: Zur Kenntnis der Nabeladenome, Acta chir. Scandinav. **62**: 310, 1927.

5. Weller, quoted by Jacobsen, V. C.: Ectopic Endometriosis, Arch. Path. **5**: 1054, 1928.

growths in the pelvis. In his opinion, the occurrence of these tumors at the umbilicus throws doubt on the theories of Sampson in regard to the origin of this entire group, and seems to find its best explanation in a theory based on serosal origin.

Smooth muscle has been found by Green,[6] Mintz,[7] Goddard,[8] Barker,[9] Cullen,[10] Matthias, Munro and Bottomley,[11] Mahle and McCarty,[12] Edwards and Spencer,[13] Stacy, Drips, Offutt and Moerich,[14] Palmen,[4] and Roques,[1] and not found or not mentioned by von Noorden,[11] Giannettasio,[15] Herzenberg,[16] Ehrlich,[17] Zitronblatt,[18] Lauche,[19] Tobler,[20] Keitler,[21] Schiffman and Seyfert,[22] Le Lievre and

6. Green, C. D.: A Case of Umbilical Papilloma Which Showed Some Activity of Growth in a Patient Fifty Years of Age, and Which Was Due Apparently to the Inclusion of a Portion of Meckel's Diverticulum, Tr. Path. Soc., London **50**:243, 1898-1899.

7. Mintz, W. M.: Das wahre Adenom des Nabels, Deutsche Ztschr. f. Chir. **51**:545, 1899.

8. Goddard, S. W.: Two Umbilical Tumors of Probable Uterine Origin, Surg. Gynec. Obst. **9**:249, 1909.

9. Barker, A.: Three Cases of Solid Tumours of the Umbilicus in Adults, Lancet **2**:128 and 130, 1913.

10. Cullen, T. S.: The Umbilicus, Philadelphia, W. B. Saunders Company, 1916.

11. Quoted by Cullen (footnote 10).

12. Mahle, A. E., and MacCarty, W. C.: Ectopic Adenomyoma of the Uterine Type, J. Lab. & Clin. Med. **5**:218, 1919.

13. Edwards, C. R., and Spencer, H. R.: Adenomyoma of the Umbilicus, Arch. Surg. **11**:684, 1925.

14. Stacy, L. J.; Drips, D. G.; Offutt, S. R., and Moerich, L. M.: Adenomyoma of the Umbilicus, M. Clin. North America **10**:677, 1926.

15. Giannettasio, N.: Sur les tumeurs de l'ombilic, Arch. gén. de méd. **3**:52, 1900.

16. Herzenberg, R.: Ein Beitrag zum wahren Adenom des Nabels, Deutsche med. Wchnschr. **35**:889, 1909.

17. Ehrlich, H.: Primäres doppelseitiges Mammacarcinom und wahres Nabeladenom; ein Beitrag zur Beurteilung multiplier Tumoren, Arch. f. klin. Chir. **89**: 742, 1909.

18. Zitronblatt, A.: Zur Kasuistik und Histogenese der Nabeladenom, Deutsche med. Wchnschr. **39**:371, 1913.

19. Lauche, A.: Die extragenitalen heterotopen Epithelwucherungen vom Bau der Uterusschleimhaut, Virchows Arch. f. path. Anat. **243**:398, 1923; Zur Pathologie der Nabelgegend, Verhandl. d. deutsch. path. Gesellsch. **19**:341, 1923.

20. Tobler, T.: Ueber tumorartige entzündliche Uterindriesen ähnliche Wucherungen des peritoneal Epithels in Laparotomienarben und über ebensolche spontan Wucherungen im Nabel, Frankfurt. Ztschr. f. Path. **29**:558, 1923.

21. Keitler, H.: Ueber einem Fall von Nabeladenom, Monatschr. f. Geburtsch. u. Gynäk. **64**:171, 1923.

22. Schiffman, J., and Seyfert, W.: Ein Nabeladenom, Arch. f. Gynäk. **127**: 208, 1925.

Montpellier,[23] Oberling and Hickel,[24] Kohler,[25] Andrews,[26] Steiner,[27] Busser [28] and Baltzer.[29] Fraser [30] reported finding an endometrioma of the umbilicus in *Macacus rhesus* and some twenty-three endometriomas in the peritoneal cavity of the same monkey. The umbilical tumor did not contain smooth muscle, nor was it connected with the peritoneum. The peritoneum has been reported to be connected with the umbilical tumor by Giannettasio,[15] Barker,[9] Mintz,[7] Herzenberg,[16] Waegelin,[31] and Tobler.[20] The latter recorded a deep, funnel-shaped diverticulum of the peritoneum to which the tumor was attached. Roques [1] described a peritoneal fold similar to the one found in the specimen reported here. The great majority recorded bleeding at menstruation, and sometimes painful swelling and bluish discoloration. The tumor is found most often in women between 35 and 45 years of age. The patient whose case is reported here was the youngest on record to have had a tumor of this type. Kohler,[25] in 1927, reported what he claimed was the thirty-second case on record. Since that date nine cases, including the one reported here, have been recorded, bringing the total number to forty-one.

SUMMARY

A case of endometriomyoma of the umbilicus is described. The tumor was composed of glands and stroma similar to endometrium and smooth muscle. Two mucus-secreting glands were found in the tumor. Glands were discovered and traced to the peritoneum. Evidence is offered in favor of the local origin of the tissue. Both the theory of serosal origin and that of congenital misplacement may be used to explain the origin of the heterologous tissue, since there is some evidence in favor of each. The transplantation theory does not seem to be applicable to tumors like this one. The immediate origin from a remnant of the omphalomesenteric duct is likewise unlikely. A remote origin from the tissues forming the omphalomesenteric duct is possible.

23. Le Lievre and Montpellier: Sur un cas d'endometriome de la region ombilicale, Bull. Assoc. franç. p. l'étude du cancer **16**:867, 1927.

24. Oberling, C., and Hickel, P.: Le probleme de l'endometriome. A propos de deux cas nouveaux (intestin et ombilic), Bull. Assoc. franç. p. l'étude du cancer **16**:691, 1927.

25. Kohler, R.: Adenomyosis des Nabels, Zentralbl. f. Gynäk. **51**:2201, 1927.

26. Andrews, H. R.: A Case of Endometrioma of the Umbilicus, J. Obst. & Gynaec. Brit. Emp. **32**:545, 1925.

27. Steiner, H.: Ein Nabeladenom, Zentralbl. f. Gynäk. **51**:2796, 1927.

28. Busser, F.; Van der Horst, and Dronhard: Endometriome de l'ombilic, Ann. d'anat. path. **5**:229, 1928.

29. Baltzer, H.: Ueber heterotope endometrioide Wucherungen ins besondere am Nabel ("Nabeladenom"), Zentralbl. f. Gynäk. **53**:99, 1929.

30. Fraser, A. D.: Ectopic Endometrium in Macacus Rhesus, J. Obst. & Gynaec. Brit. Emp. **36**:590, 1929.

31. Waegelin, H.: Zur Histogenese der Nabeladenom nebst einem kasuistischen Beitrag, Frankfurt. Ztschr. f. Path. **14**:367, 1913.

THE VARIATION IN WEIGHT OF THE THYROID GLAND AND THE FREQUENCY OF ITS ABNORMAL ENLARGEMENT IN THE REGION OF CHICAGO*

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CHICAGO

The statistical reports on the frequency and geographic distribution of goiter in the United States are based chiefly on the systematic examination of certain parts of the population in which such examination can be easily carried out, as for example school children, university students and men encamped through military draft. Valuable as the results of these surveys of goiter are, they do not satisfy fully, because in them all age groups are not considered to the same extent, and because they involve a variable factor in the ability, special training and experience of the examining physician. Furthermore, no information is given in them as to the type of goiter. Anatomic studies of the thyroid gland are therefore of great value in completing the data collected by examination of the living. Against anatomic studies, the objection may be made that the cause of death may have influenced the weight and structure of the gland, and that hence the results could not be applied to the healthy population. The weight of the thyroid gland, however, decreases only in chronic wasting diseases, and this decrease is part of the atrophy of the other organs. The circumscribed enlargements of the thyroid gland in the form of nodes are apparently not affected. Critical selection of the material will therefore meet with this objection.

MATERIAL OF STUDY

The present study is based on the examination of the thyroid gland in 1,000 autopsies. Cases in which there was marked atrophy of the internal organs were excluded. The thyroid was dissected out and, after being weighed, was cut into parallel, sagittal sections about 0.5 cm. apart and examined for the presence of nodules and nodes. The material was divided into two groups. One group contained the glands that were free from nodes, while the other group was composed of the glands with nodes.

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* From the Department of Pathology, Cook County Hospital.

According to age, sex and race, the glands were distributed as shown in table 1. In addition there were thyroid glands from twenty-eight Mexican men and from twenty-two Mexican women.

THE AVERAGE WEIGHT OF THE THYROID GLAND IN THE REGION OF CHICAGO

Before the frequency of enlargement can be determined, it is necessary to determine the average weight of the thyroid gland. For compiling this weight, only glands without nodes were used. In my series of cases, the weight of the thyroid gland in the first year of life was about the same as that reported from Germany (Wegelin [1]), France (Tourdes,[2] Testut [2]) and Italy (Cavaloni,[3] Maedele [3]). There is no marked difference in weight of the thyroid gland at this age between

TABLE 1.—*Distribution of the Thyroid Glands Studied*

	Number of Thyroid Glands				
	White Race		Colored Race		
Age Period	Male	Female	Male	Female	Total
0- 1	9	9	11	8	37
1- 6	13	12	10	10	45
7-17	14	14	12	11	51
18-21	4	6	6	6	22
22-30	18	16	36	31	101
31-40	48	40	48	26	162
41-50	104	27	52	25	208
51-60	85	19	28	9	141
61-70	76	25	18	14	133
Above 70	34	10	4	2	50
Total	405	178	225	142	950

the two races. The gland in the females is slightly larger than that in the males. This difference disappears in childhood. During puberty there is a rapid growth of the thyroid gland in both the males and the females. The weight of the thyroid gland increases slightly after the growth of the body has ceased, and in white males reaches a maximum in the third decade. Then, under fluctuation, it decreases to start a new rise in the fifth decade. May [4] also stated that the thyroid gland of the male becomes enlarged after the age of 50, a new proliferation that does not occur in the female. The weight curves of the Negro's thyroid gland is somewhat different; it reaches its maximum in the sixth decade, after which it shows a rather sharp decline. The weight curve of the thyroid gland of the white woman is highest

1. Wegelin, C.: Schilddruese, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie, Berlin, Julius Springer, 1926, vol. 8.

2. Quoted by Wegelin (footnote 1).

3. Quoted by Riddle, O.: Endokrinologie **5**:241, 1929.

4. May, H.: Arch. f. klin. Chir. **149**:501, 1928.

between the ages of 30 and 50, when it is slightly above that of the white man. Later, it drops continuously. In colored women, the curve runs almost parallel, but at a lower level. The average weight of the thyroid gland in white men is 27.4 Gm.; in colored men, 27.4 Gm.; in white women, 28.1 Gm., and in colored women, 24.6 Gm. The Mexicans were too few to be subdivided into age groups, and therefore only the average weight of the thyroid gland according to sex is given: 23 Gm. for males and 26 Gm. for females.

In the literature on the thyroid gland, the figures for the weight vary considerably. Thus, Vierordt [5] in his anatomic physiologic tables gave the weight as 33.8 Gm., Orth [6] as from 30 to 60 Gm., Marchant [7] as from 22 to 24 Gm., Guiart [7] as 25 Gm., Wegelin [1] as from 20 to 25 Gm., Carlaldy as from 16 to 21 Gm., Lucien, Parisot and Richard [8] as 35 Gm., Crile [9] as from 25 to 40 Gm. and Schaer [10] as 26.4 Gm. for

TABLE 2.—*Average Weight of Thyroid Gland*

	Average Weight of Thyroid Gland, Gm.			
	White		Colored	
Age Period	Males	Females	Males	Females
0- 1	1.6	2.6	1.9	2.9
1- 6	5.2	5.4	4.8	5.1
7-17	13.2	15.4	15.7	15.3
18-21	22.3	20.8	19.5	23.6
21-30	28.6	26.7	25.2	24.3
31-40	29.8	31.7	25.7	25.4
41-50	26.5	31.0	29.0	24.5
51-60	27.5	21.2	30.8	22.3
61-70	23.3	19.5	31.4	21.4
Above 70	26.0	16.0	23.3	21.0

the male gland and 25.5 Gm. for the female gland. According to Osaki,[3] Horisawa [2] and others, the thyroid gland of the Japanese is smaller than one would expect from the length of body of this race; the gland is only a little more than half the size of that of the white race.

DIFFUSE ENLARGEMENT OF THE THYROID GLAND

In all the age groups there is considerable variation in the weight of the thyroid gland, which in my series amounts to from 15 to 140 Gm. This holds true for both races and both sexes. It is there-

5. Vierordt: Daten und Tabellen, Jena, Gustav Fischer, 1893.

6. Orth, J.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, 1887, vol. 1.

7. Guiart: Thèse de Paris, 1896.

8. Lucien, M.; Parisot, J., and Richard, G.: Traité d'endocrinologie, Paris, G. Dorin, 1925.

9. Crile, G. W., and associates: The Thyroid Gland, Philadelphia, W. B. Saunders Company, 1923.

10. Schaer, H.: Frankfurt. Ztschr. f. Path. **36**:249, 1928.

fore difficult to fix a definite weight above which the gland is to be considered enlarged. The figures in the table on the frequency of diffuse enlargement of the thyroid gland are based on a weight above 40 Gm. It is not so much the weight that induces me to regard these glands as goitrous as it is their structure. The glands show the macroscopic and microscopic picture of diffuse colloid goiter. They are rich in colloid and are composed of large colloid-filled follicles with slight or without proliferative changes.

The diffuse colloid goiter is most common in persons below the age of 50. In white males the greatest frequency is found in the second and third decades of life, and in colored males in the fourth decade of life. There is a distinctly greater frequency among the males than among the females; in my series, no diffuse colloid goiter was found in a white or colored woman past the age of 50.

TABLE 3.—*Percentage of the Thyroids Weighing Above 40 Gm.*

	White, Per Cent		Colored, Per Cent	
Age Period	Males	Females	Males	Females
18-21	25.0	16.6	....	....
22-30	16.6	12.5	11.1	9.6
31-40	16.6	12.5	12.5	11.5
41-50	11.5	7.4	15.3	12.0
51-60	11.7	....	14.2	....
61-70	6.5	....	11.1	....
Above 70	6.2	....	....	....
All age periods	11.3	8.7	11.2	7.8

In regions of endemic goiter, diffuse enlargement of the thyroid is much less common than the nodose type. Wegelin (Bern) gave the percentage as 11.6 and Hellwig [11] (Freiburg in Breisgau) as 4.02 per cent. Wegelin did not find the difference between the sexes that I observed.

NODOSE ENLARGEMENT OF THE THYROID GLAND

The youngest person presenting a nodose goiter, in my series, was a white girl aged 12; then there were a colored boy 14 years of age and a white boy 15 years of age. In all four groups there is a constant increase in the frequency of the nodose enlargement of the thyroid gland with progressing age, but the rate of this increase shows marked differences. The sharpest rise is found in white women; the thyroids of two thirds of the white women past the age of 60 contain nodes. In colored women, the highest level is reached at the ages of from 61 to 70. In the seventh decade there is a decrease. In white and colored men, the

11. Hellwig, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **32**:508, 1920.

increase is much more gradual and lies distinctly below that in the female sex. The difference is greatest in the age groups above 40.

There is a difference in the frequency of nodose goiter between the white and the colored race, especially if all the age groups are taken together. It is then found that the percentage of nodose goiter in white males is 30, in colored males 14.5, in white females 44.7 and in colored females 25.5.

Hellwig,[12] discussing the type of North American goiter, stated that in his surgical material the weight of the goitrous gland is on an average from 80 to 100 Gm. This is slightly more than I have observed at autopsy. The gland with nodes usually is heavier than the gland without nodes, but weights above 100 Gm. are rare. In my series, there were only twenty goiters the weights of which were above 100 Gm. and five the weights of which were above 200 Gm. These large glands were found only in women. The weight of the largest gland was

TABLE 4.—*Percentage of Nodose Goiters*

	White, Per Cent		Colored, Per Cent	
Age Period	Males	Females	Males	Females
18-21	....	....	2.0	....
21-30	5.5	18.7	5.5	6.4
31-40	22.8	30.0	12.5	15.3
41-50	23.0	40.7	11.4	32.0
51-60	29.4	63.2	17.9	44.0
61-70	46.0	72.0	33.0	78.5
Above 70	44.1	80.0	25.0	50.0

400 Gm. It was found in a white woman, aged 71. Most of the nodes were small, averaging from 5 to 20 mm. in diameter; only 5 per cent of the nodes were more than 30 mm. in diameter.

COMMENT

The Cook County Hospital draws its material chiefly from the west side of Chicago. Composed only of charity patients, this material represents the lower classes of the population. The patients come from all parts of the world, but most of them have spent the greater part of their lives in Chicago or its vicinity. With certain reservations, the results obtained in this study can be considered as typical of the largest city of the region of the great lakes, which is one of the districts of the United States in which the incidence of goiter is large.

In some of the age groups, especially those below the age of 22, my material is small, but it is surprising that among 103 children of both sexes and races there were only 17 with goiters. Of these children, 13.3 per cent showed a diffuse enlargement of the thyroid gland and 2.9 per cent a nodose goiter. These figures are much lower than those

12. Hellwig, A.: Arch. f. klin. Chir. **154**:1, 1929.

given by Olesen [13] in his statistics on the distribution of goiter in the United States, namely, from 6.7 to 25.8 per cent for Chicago boys and from 17.8 to 43.3 per cent for Chicago girls.

Comparing my results with a large body of anatomic statistics on a highly goitrous population of central Europe (Bern, Switzerland, according to Wegelin), I find that the figures for Chicago are much the lower. Wegelin observed nodose goiters in 73.3 per cent of the men above 20 years of age and in 88.4 per cent of the women above this age, as compared with 30 and 44.7 per cent in my statistics. Among 800 people submitting themselves to a medical examination for a position in the civil service in Chicago, Olesen [14] found goiters in from 15.36 to 20.38 per cent of the women and in 6.72 per cent of the men.

In Bern, in practically every person above the age of 50 the thyroid gland contains nodes (Clerc). In Freiburg in Breisgau (southern Germany), Kloeppels [2] found the incidence of nodose goiter in persons past the age of 50 to be 81 per cent. In other regions of Germany in which goiter is endemic, Heilmann [15] saw nodose goiters in 40 per cent of the population. Nodose goiter also occurs in regions free from endemic goiter. The formation of the nodes, however, seems to start much later in life than it does in the regions in which goiter is endemic.

All investigators agree that goiter is more common in the female sex than in the male sex. Biedl [8] gave the ratio as 4:1; Hertzler [16] as from 6:1 to 10:1; Youmans [17] as 4:1. McCarrison [18] said, "Where the endemicity is slight, cases may be met with only among women, but in regions of high endemicity the proportion of women to men affected may approximate as closely as one to one." The difference in frequency of nodose goiter between the female and the male sex is most marked between the ages of 51 and 60. Between these ages, nodose goiter is more than twice as common in women as in men. For all age groups together, the relation is 1.4:1, for the white race, and 1.8:1 for the colored race.

While the frequency of nodose goiter increases with advancing age, that of diffuse goiter decreases. Diffuse goiter is more common in males and nodose goiter in females.

In regions of endemic goiter, the nodose outnumbers by far the diffuse enlargement. In Bern, 93 per cent of the goiters are nodose; in Freiburg in Breisgau, 77 per cent. In regions without endemicity,

13. Olesen, R.: Pub. Health Rep. **44**:1463, 1929.

14. Olesen, R.: Illinois M. J. **27**:16, 1915.

15. Heilmann, P.: Virchows Arch. f. path. Anat. **251**:361, 1924.

16. Hertzler, A. E.: Diseases of the Thyroid Gland, St. Louis, C. V. Mosby Company, 1922.

17. Youmans, J. B.: South. M. J. **22**:966, 1929.

18. McCarrison, R.: The Thyroid Gland, London, 1917.

the diffuse goiters prevail. Thus, in Frankfurt-on-Main, the percentage of diffuse goiters is 56 and in Goettingen 65. Among the goiters of the Hertzler clinic at Halstead, Hellwig found 53 per cent diffuse and 47 per cent nodose. Of the goiters in my series, 69.3 per cent are of the nodose type.

An interesting observation is the distinctly greater disposition to nodose goiter of the white race as compared with the colored race. In white males, this form of goiter is twice as common as in colored males, and in females the difference is but slightly less. It is only in the age groups above 50 that the percentage of the colored women approached that of the white women.

Youmans, who examined 500 patients of the outpatient department of the University Hospital at Nashville, Tenn., found the incidence of goiter to be less in the colored than in the white subjects, except for certain age periods. Olesen,[19] however, saw less goiter among the white than among the colored children in Tennessee. In New York, Cohen [20] and Goldberger and Aldinger [21] reported less goiter among the colored children. According to Jones,[22] goiter is less common among the Negroes of Atlanta than among the whites.

Among Indians, the incidence of goiter parallels that among the white population (Rush and Jones [23]). My material is too small to allow any statement about the frequency of goiter among Indians. None of the Mexicans whom I examined showed a goiter, but most of these Mexicans had been in Chicago less than ten years.

Among the 1,000 persons on whom autopsies were performed, 3 died from hyperthyroidism and 2 from carcinoma of the thyroid.

SUMMARY

The average weight of the thyroid gland in the region of Chicago is, for white men, 27.4 Gm.; for white women, 28.1 Gm.; for colored men, 27.4 Gm.; for colored women, 24.6 Gm.; for Mexican men, 23 Gm., and for Mexican women, 26 Gm.

The greatest weight of the thyroid gland is found in white men between the ages of 20 and 30, in colored men between the ages of 50 and 60, in white women between the ages of 30 and 50 and in colored women between the ages of 30 and 40.

19. Olesen, R.: Pub. Health Rep. **44**:865, 1929.

20. Cohen, F.: Goiter in Children in New York City: Thyroid Survey of 11,084 School Girls and 783 School Boys, Am. J. Dis. Child. **31**:676, 1926.

21. Goldberger, I. H., and Aldinger, A. K.: Goiter Incidence in School Girls of New York City, Am. J. Dis. Child. **29**:780, 1925.

22. Jones, E. G.: Goiter, J. A. M. A. **71**:712, 1918.

23. Rush, H. P., and Jones, L. F.: Endocrinology **9**:372, 1925.

Diffuse enlargement of the thyroid gland is more common in persons below the age of 50 than in those above this age. It is more frequent in the male than in the female sex. There are no differences in its incidence as between the two races.

The frequency of nodose goiter increases with advancing age. It reaches its maximum in white men in the sixth, in white women in the seventh, in colored men in the sixth and in colored women in the sixth decade of life. Nodose goiter is more common in females than in males, and there is a greater disposition to it in the white race than in the colored race. The percentages for nodose goiter are: white males, 30; white females, 44.7; colored males, 14.5, and colored females, 25.6.

Sixty-nine and three-tenths per cent of goiters are nodose.

The majority of nodose goiters are of moderate size; weights above 100 Gm. are rare. The nodes are usually small, seldom reaching a diameter above 4 cm.

General Review

ADDISON'S DISEASE

A STATISTICAL ANALYSIS OF FIVE HUNDRED AND SIXTY-SIX CASES AND A STUDY OF THE PATHOLOGY

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(Concluded from p. 785)

CORRELATION BETWEEN SYMPTOMS AND ANATOMIC CHANGES

A description of the various symptoms of the disease will not be covered in this paper, as little can be added to the excellent works of Addison, Greenhow, Wilks, Lewin, Bramwell, Neusser, Bittorf, Rolleston, Rowntree, Snell and Rowntree and others. However, an attempt will be made to correlate the various symptoms with the pathologic changes in the suprarenal gland, and also to discuss the relative importance of the medulla and of the cortex in the production of the syndrome.

BILATERAL TUBERCULOSIS OF THE SUPRARENAL GLANDS WITHOUT SYMPTOMS OF ADDISON'S DISEASE

Bilateral tuberculosis of the suprarenal glands without symptoms of Addison's disease is reported from time to time in the literature. Laignel-Levastine and Halbron reported three cases. Alezias and Arnard, in a study of case reports of Addison's disease, found a number of instances in which bilateral disease of the suprarenal glands existed without clinical manifestations. Other cases were reported as follows: Von Kahlden, six cases; Goldschmidt, two cases; Cabot, Boyd, Stürsberg, Crowell and Karpeles, each one case. Keros and Rolleston reported forty-four cases, and Lewin cited sixty-four cases; the extent of involvement in these, however, was not given. Of thirty-four cases of bilateral tuberculosis that came to autopsy at the University of Minnesota, six cases showed absence of symptoms of Addison's disease. The case described in the following section is given because of its unusual clinical course.

CASE A-27-1179.—*History.*—A colored woman, aged 51, was admitted to the Minneapolis General Hospital on Sept. 8, 1927, complaining of shortness of breath, swelling of the legs and tumor of the abdomen. Swelling of the feet had been present for five months. Nocturia two or three times was present for one month; the bowels were regular; the appetite was good. The father died of tuberculosis three years previously; otherwise, the family history was irrelevant.

Examination.—Physical examination showed: coated tongue; cervical adenopathy; hyperresonance in the lower portion of both lungs; increased breath sounds; diffuse apex beat of the heart; maximum impulse in the sixth interspace in the anterior axillary line; a pulse rate of 142; blood pressure 192 systolic and 128 diastolic, and a large tumor filling the greater part of the abdomen.

Laboratory report gave: specific gravity of the urine, 1.034; albumin, one plus; sugar, absent; hyaline and granular casts, many; red blood cells and white blood cells, few; red blood cells, 3,500,000; leukocytes, 3,950; lymphocytes, 44 per cent; neutrophils, 52 per cent; eosinophils, 2 per cent; monocytes, 3.2 per cent; urea nitrogen of the blood, 9.3 mg.

Course.—Compensation of the heart returned in from two to three weeks. The patient was able to get up and around. On November 11, operation for removal of the fibroid tumor was advised to relieve the cardiac strain. The blood pressure before operation was 208 systolic and 134 diastolic. The patient died suddenly on the operating table during the administration of caudal anesthesia via the sacral hiatus.

Necropsy.—The body was that of a well developed, obese colored woman. Slight edema was shown about the ankles. A large, pedunculated fibroid tumor, weighing 3,400 Gm., was attached to the uterus. There was 400 cc. of fluid in the abdomen. The heart weighed 600 Gm.; there was marked hypertrophy of the left ventricle; the valves were normal; the myocardium was normal; there was slight thickening of the coronary arteries. The root of the aorta showed moderate atheromatous degeneration of the intima. The right lung presented marked edema; it weighed 950 Gm. The left lung appeared normal. There was moderate enlargement of lymph nodes at the hilus of the lungs; no calcification or caseous degeneration was shown. Large calcified lymph nodes were seen in the mesentery.

The right suprarenal gland weighed 32 Gm.; it was firm and nodular, and cut with increased resistance. The substance was entirely replaced by irregular caseous areas, which were separated by grayish connective tissue and areas of dark red, less firm tissue. The left suprarenal gland weighed 24 Gm. and showed similar changes. The kidneys showed a finely granular surface and moderate atrophy of the cortex.

Microscopic Examination.—The suprarenal glands showed the parenchyma largely replaced by irregular conglomerate caseous areas, about which there was a fairly marked reaction of epithelioid cells, an extensive infiltration of lymphocytes and a diffuse fibroblastic proliferation. There was a marked diffuse lymphocytic infiltration in wide zones about the caseous areas. Small areas of fairly well preserved cortical cells consisting of the zona glomerulosa and peripheral portions of the zona fasciculata were present here and there. The capsule showed an extension of the tuberculous process at many points with the involvement of the pericapsular tissue. Ziehl-Nielsen stain showed many scattered groups of tubercle bacilli near the periphery of the caseous areas.

In this case there was no evidence of Addison's disease during life, but the symptoms were mainly those of cardiac failure secondary to hypertension. The blood pressure on the day of death was 210 systolic and 110 diastolic. Death occurred suddenly during caudal anesthesia.

In many of the cases reported in the literature, death occurred suddenly and without apparent cause. It is not uncommon for the patient to complain of severe abdominal pain, and often the abdominal pain is so severe that it is mistaken for acute appendicitis. Operative inter-

vention in these cases is usually fatal. In another group of cases, the symptoms of suprarenal involvement are masked by widespread tuberculosis of the lung or some other debilitating disease.

The extent of involvement of the suprarenal gland cannot be determined from the cases in the literature. A comparison was made of those cases showing bilateral tuberculosis of the suprarenal glands without symptoms of Addison's disease and those in which symptoms are clearly manifested. These are given in the first instalment of the article which appeared in the November issue, p. 753. Although accurate estimate of the surviving tissue cannot be made because of the widely and irregularly scattered fragments of cortical tissue, it is probable from the evidence at hand that sufficient cortical tissue remains to offset symptoms of the disease.

It is apparent that while a large percentage of patients with bilateral tuberculosis of the suprarenal glands have symptoms of Addison's disease, there are many in whom the symptoms are lacking. Many observers are inclined to regard the pathologic changes as synonymous with Addison's disease. This is erroneous, as Addison did not describe a pathologic condition but a clinical syndrome associated with destructive lesions of the suprarenal glands. The term latent tuberculosis of the suprarenal glands was introduced by Oppenheim and Loeper,[487] and Laignel-Lavastine and Halbron. This term is satisfactory, but should be used in a clinical sense only, as the lesions in the suprarenal glands in most cases are active and progressive.

DURATION OF THE DISEASE AND AGE OF THE PATIENT

It is frequently stated that Addison's disease tends to run a more rapid course in the young than in older persons. An analysis of the cases collected from the literature does not support this idea. A correlation chart (fig. 12) was made in which only those cases are included in which the duration of the disease and the age of the patient are definitely stated. There are 178 cases available for this analysis.

The correlation coefficient is 0.060 with a probable error of 0.050. The average of the duration is plotted and represented by the coarse continuous line. It is irregular and roughly parallels the mean represented by the horizontal line. It is therefore evident that there is no correlation between the duration of the disease and the age of the patient.

DURATION OF THE SYMPTOMS AND THE TYPE OF LESIONS IN THE SUPRARENAL GLAND

In 194 cases in which autopsy records are given, the duration of the disease is definitely stated in years or months. These are divided into three groups (table 13). Group 1 consists of acute cases that are

of two months' or less duration; group 2, of subacute cases that are of less than six months' but more than two months' duration, and group 3, of chronic cases of more than six months' duration. The frequencies of suprarenal tuberculosis, primary contracted suprarenal gland, amyloid disease and other lesions are given.

There are fifteen cases, or 12.10 per cent of all cases of tuberculosis of the suprarenal glands, in which the duration of the disease is given as of less than two months' duration. This is much greater than the number of acute cases of primary contracted suprarenal gland, of which only two cases, or 3.92 per cent, are reported. The percentage of subacute cases is also higher in the tuberculosis group than in the primary

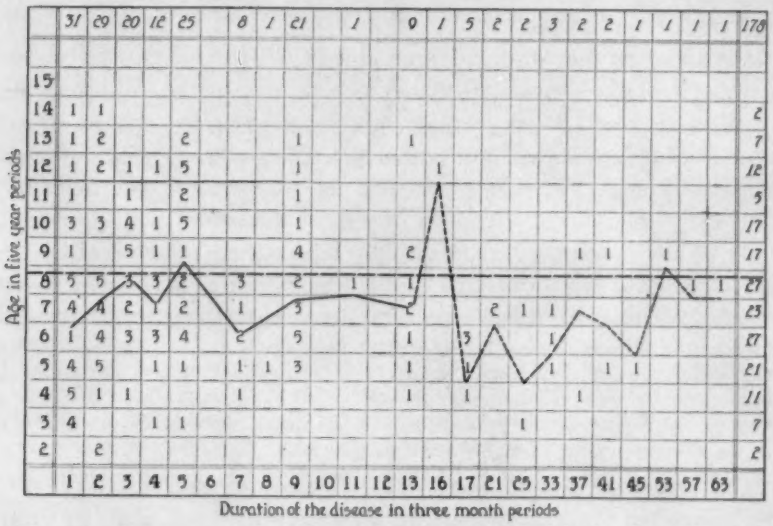

Fig. 12.—Chart correlating the age of the patient with the duration of Addison's disease. The average of the duration is represented by the solid line. The mean is represented by the horizontal line.

contracted suprarenal group. There are forty-two cases, or 33.87 per cent, in the former, and fifteen, or 39.41 per cent, in the latter. The percentage of chronic cases of primary contracted suprarenal gland is much higher than the percentage of chronic cases of tuberculosis of the suprarenal glands. Cases with amyloid disease tend to run a more chronic course than cases with vascular lesions. There are two cases in the subacute group and two in the chronic group in the former, and two in the acute group and two in the subacute group in the latter.

In order to determine whether the difference of duration in the cases of suprarenal tuberculosis and cases of primary contracted suprarenal glands is significant, the mean of each group and the probable error of their difference are determined. The mean duration of the

cases of tuberculosis of the suprarenal glands is 13.31 ± 2.54 months, and that of primary contracted suprarenal gland is 34.02 ± 4.40 months. The probable error of the difference of the means is 5.10. The difference between the means is more than four times its own probable error and, therefore, can be considered significant.

TABLE 13.—*Duration of Addison's Disease in Relation to Type of Lesion*

Type of Cases	Tuberculosis		Primary Contracted Suprarenal Gland		Amyloid Disease		Vascular Disease		Other Lesions		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	
Acute*	15	12.1	2	3.9	0	0	2	50	1	9.1	20
Subacute†	42	33.9	15	29.4	2	50	2	50	3	27.3	64
Chronic‡	67	54.0	34	66.7	2	50	0	0	7	63.6	110
Total	124	100.0	51	100.0	4	100	4	100	11	100.0	194

* Of two months' or less duration.
† Of less than six months' but more than two months' duration.
‡ Of more than six months' duration.

TABLE 14.—*Duration of Addison's Disease in Relation to Tuberculosis and Suprarenal Contracted Suprarenal Gland*

	Duration
Cases of tuberculosis of the suprarenals	
Cases in which the exact duration is given	
Ferrando and Saloz	8 years
Crowell	11 years
Cases of long duration in which exact duration is not given	
Scheult	Many years
Sakaguchi and associates	Several years
Schür (case 2)	Always dark
Withington (case 1)	Always dark
Löffler	Several years
Kahn	Pigmentation since childhood
Germain	Pigmentation always present
Cases of primary contracted suprarenal gland in which the duration is longer than five years	
Cases in which the exact duration is given	
Phillips	14 years
Münzer	9 years
Fahr and Reiche	8 years
Kiefer	15 years (?)
Held	10 years
Lucksch	9 years
Karakascheff	8 years
University of Minnesota (case 2)	15 years
Conybeare and Millis	10 years
Other cases of which duration is questionable or not stated	
Wakefield and Smith	Pigmentation since birth
Scott	Pigmentation since birth
Medlar	19 years (?)
Green	Always pigmented

There are nine cases of primary contracted suprarenal gland, or 17.65 per cent, having a duration greater than sixty months, and only two cases of tuberculosis of the suprarenal glands, in which the duration is greater than sixty months. These are listed in table 14, with the names of the recorders.

DURATION OF SYMPTOMS OF ADDISON'S DISEASE IN CASES OF ACTIVE AND MARKED TUBERCULOSIS IN THE BODY OTHER THAN IN THE SUPRARENAL GLANDS, AND IN CASES IN WHICH THE LESIONS ARE HEALED OR MINIMAL

The effect of marked lesions in other parts of the body on the suprarenal glands cannot be determined in this study. It is probable that marked lesions exert a toxic effect on the surviving cells in the suprarenal glands. Oppenheim and Loeper [486] showed that by injecting dead tubercle bacilli into animals, marked necrosis of the suprarenal glands can be produced. Omelskyj and Kovacs held that, in man, in addition to the lesions caused by the tubercle bacilli, hyalinization and even necrosis of the suprarenal glands may be produced by the toxic products of a tuberculous lesion elsewhere. Bernard and Bigart, and Kioyokawa described a perivascular sclerosis, an increase in the amount

TABLE 15.—*Deviations in Duration of Addison's Disease with Relation to Extrasuprarenal Tuberculosis of Marked Activity (Group 1) and of Healed or Minimal Stages (Group 2)*

	Group 1	Group 2
Maximum	48 months	96 months
Minimum	1 month	0.5 month
Mean	12.04 ± 1.33 months	14.40 ± 1.60 months
Standard deviation	11.65 ± 0.94 months	16.82 ± 1.14 months

of connective tissue and even replacement of the parenchyma by connective tissue in cases of marked tuberculous lesions in other parts of the body.

To determine whether these factors influence the course of the disease, all cases of Addison's disease with tuberculosis of the suprarenal glands were placed in two groups. Group 1 contained thirty-five cases in which there was marked extrasuprarenal tuberculosis; group 2 contained fifty cases in which the lesions elsewhere were healed or minimal. The maximum, minimum, mean and standard deviations are as given in table 15.

The probable error of the difference of the two groups is 2.088. The difference between the means is 2.35, which is 1.3 times its probable error. This cannot be considered significant.

DURATION OF THE DISEASE AND NATURE OF THE ONSET OF SYMPTOMS

In many cases it has been observed that if pigmentation is present to a marked degree in the absence of other symptoms, the duration of the disease is exceedingly long. Also it has been noted that in cases in

which weakness is the dominant symptom and no pigmentation is present, the duration of the disease is exceedingly short. This fact was first noted by Fenwick in 1898. He collected thirty-three cases from the literature and observed that the duration of the cases in which marked bronzing of the skin was shown averaged 23.5 months, and that the average duration of the cases in which bronzing was absent was from four to eight months.

Marañon, in a recent article, divided his cases into two forms, a primary and a secondary form. In the primary form, pigmentation is slight, as compared with the other symptoms, and the course of the disease is rapid. In the secondary form, the pigmentation is marked, and the course of the disease is markedly long.

TABLE 16.—*Duration of Addison's Disease and Nature of Onset of Symptoms*

Duration in Months	Group A*		Group B†		Group C‡	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
0 to 3	1	1.64	10	22.22	21	46.66
4 to 7	8	13.11	13	28.89	9	20.00
8 to 11	2	3.28	4	8.89	4	8.89
12 to 15	12	19.67	7	15.56	3	6.67
16 to 19	4	6.56	2	4.44	0	0.0
20 to 23	3	4.91	0	0.0	0	0.0
24 to 27	5	8.20	5	11.11	4	8.89
28 to 31	0	0.0	0	0.0	0	0.0
32 to 35	0	0.0	0	0.0	0	0.0
36 to 39	5	8.20	1	2.2	4	8.89
40 to 43	1	1.64	0	0.0	0	0.0
48 to 51	4	6.56	3	6.67	0	0.0
60 months and over	16	26.23	0	0.0	0	0.0
Total	61	100.00	45	100.00	45	100.0

* First symptom of onset is pigmentation.
† Pigmentation and weakness appear simultaneously.
‡ Weakness is the predominant symptom at onset.

In collecting the literature, the exact duration of the disease and the degree of pigmentation was carefully noted in all cases. While it is true that the onset of the disease is insidious and in the majority of cases the exact duration cannot be determined, a sufficient number of cases is available in which the exact onset of the pigmentation and weakness is given. Cases in which there was any doubt as to the exact duration of the various symptoms were rejected.

These cases are classified as follows: Group A consists of sixty-one cases in which the first symptom is pigmentation; weakness is absent at first, and of late occurrence; group B consists of forty-five cases in which pigmentation and weakness are of simultaneous onset and about equally marked. In group C are forty-five cases in which weakness is the predominant symptom; pigmentation is absent or of subsequent onset. The frequency of these cases and the duration of the disease in four month periods are given in table 16.

The mean, the maximum, the minimum and the standard deviations are shown in table 17.

In the cases in which pigmentation is the initial and predominant symptom, the average duration of symptoms is 43.19 ± 4.3 months, as compared with 12.11 ± 1.6 months in the cases in which pigmentation and weakness are of simultaneous onset and equally marked. It is 7.71 ± 1 months in those cases in which weakness is the first symptom and in which pigmentation is lacking or of subsequent onset. The difference between the means of group A and group B is 33.213 ± 4.417. This difference is 7.5 times its own probable error and, without doubt, significant. The difference between the means of group A and group C is 31.085 ± 4.47. This is six times its own probable error and is also, without question, significant. The disease is, therefore, much longer in duration in those cases in which the pigmentation is the initial and predominant symptom than in those cases in which pigmentation of the skin and weakness are of simultaneous onset and those in which weakness is the first symptom.

TABLE 17.—*Deviations in Duration of Addison's Disease of Groups A, B and C*

	Group A	Group B	Group C
Minimum	1 month	1 month	0.25 month
Maximum	180 months	48 months	46.0 months
Mean	43.19 ± 4.3 months	12.11 ± 1.3 months	7.71 ± 1.0 months
Standard deviation	49.83 ± 3.04 months	12.35 ± 0.88 months	9.98 ± 0.71 months

It was decided to determine whether or not the degree of pigmentation, irrespective of the time of onset, has any relation to the duration of the disease. The cases are divided into four groups, according to the intensity of pigmentation of the skin. In the first group are twenty-one cases, in which there was no abnormal pigmentation of the skin; in the second group are twenty cases with slight increase of pigmentation of skin; in the third group are ninety-five cases with moderate pigmentation of the skin and pigmentation of the mucous membranes of the mouth; in the fourth group are seventy-three cases with high grade diffuse pigmentation of the skin and of the mucous membrane of the mouth. The cases are then divided into arbitrarily chosen groups, according to the duration of the disease. These are as follows: acute cases, which are of two months' or less duration; subacute cases, which are of a duration of between two and six months, and chronic cases, which are of six months' or more duration. The frequency of each group is given in table 18.

To determine whether the differences in the three groups are significant, the value of *chi* square is determined, and found to be 34.447. The value of *P*, Fischer's value for *n* being used, is 0.000022; when

Pearson's value for n is used, the value of P is 0.000688. In either case, the probability that these results could be obtained through random sampling is almost nil. The contingency coefficient is 0.3781 ± 0.1330, which confirms the foregoing statement.

To account for the prolonged duration of the disease in the cases in which pigmentation of the skin is the predominant symptom, two possibilities may be suggested: (1) that the pigmentation is a manifestation of increased secretory activity on the part of the skin, which compensates in some way for the disturbance in the secretory activity of the suprarenal glands, and (2) that the skin acts as a detoxifying agent and in this way compensates for the loss of suprarenal tissue.

Heudorfer offered some interesting suggestions in support of the first theory. He brought forth evidence that extracts of the pigment of the skin have mydriatic and pressor effects, and that, in cases of Addison's disease without pigmentation, the blood pressure tends to be

TABLE 18.—*Duration of Addison's Disease and Depth of Pigmentation of Skin*

Duration	Depth of Pigmentation of Skin				Total
	Group 0	Group 1	Group 2	Group 3	
Two months or less (acute cases)	13	5	5	0	23
Between 2 and 6 months (subacute cases)	5	9	17	9	40
Six months or more (chronic cases)	3	6	73	64	146
Total	21	20	95	73	209

very low. Also he cited a case in which there resulted a marked improvement in the condition of the patient on exposure to sunlight. with a deepening in the color of the skin. However, there is still lack of evidence that the fall of blood pressure is due to lack of epinephrine secretion (Rogoff and Dominquez, Stewart). The marked drop of blood pressure is also frequently observed in marked pigmentation and appears to parallel the development of muscular weakness.

If one accepts the theory that it is the function of the suprarenal glands to neutralize toxic products of metabolism, it may be reasonable to suppose that the skin in some way takes over this function in the process of pigmentation, and in this way prevents, for a time, the appearance of the toxemia that characterizes the later stages of Addison's disease. Since it is highly questionable that epinephrine subserves any useful function in the body, it is within reason to look on this substance as a by-product in the detoxifying process of the suprarenal gland. Stewart [504a] stated that the relative constancy of the epinephrine output and its strict regulation by the nervous system are as compatible with the view that epinephrine is a poison which must be gradually got rid of and the concentration of which in the blood must not rise above

a certain maximum, as with the view that it is a substance exercising a useful function that could not be adequately performed if the output were permitted to sink below a certain level. The fate of this substance in the tissues is not known, but evidence has been brought forth to show that it disappears rapidly in the tissues, and that it is probably converted into some inert substance. As a result of interference with the function of the gland, the precursors of epinephrine accumulate and may be transformed by the skin into less toxic substances or neutralized in the process of pigmentation.

The final solution of this interesting relation rests on a deeper knowledge of the physiology of pigmentation and its relation to the function of the suprarenal glands.

THE RELATIVE IMPORTANCE OF THE CORTEX AND OF THE MEDULLA IN THE PRODUCTION OF SYMPTOMS OF ADDISON'S DISEASE

That the symptoms of Addison's disease are due to a more or less complete destruction of the suprarenal gland is widely accepted. However, the relative importance of the cortex and that of the medulla are widely disputed. The symptoms of the disease are believed by some to be due entirely to the destruction of the cortex; by others, entirely to the destruction of the medulla, while some believe that the destruction of both cortex and medulla is responsible for the symptoms of the disease.

From his early studies Wiesel [104] concluded that the symptoms of Addison's disease are due to loss of chromaffin tissue. He based his conclusions on a study of five cases of Addison's disease in which the medulla was markedly diseased and the chromaffin tissue entirely lacking. He considered of special significance another case in which destruction of the suprarenal gland occurred without symptoms of Addison's disease, but in which the extrasuprarenal chromaffin tissue was intact.

Karakascheff [49] was directly opposed to this theory, believing that the cortex is solely responsible for all the symptoms. He pointed out that in Wiesel's cases of extensive destruction of the gland without symptoms of the disease, accessory cortical nodules were present, the significance of which Wiesel failed to emphasize. Further, he stated that, since the chromaffin organs along the course of the sympathetic ganglions normally undergo retrogressive changes shortly after birth, he failed to understand why their absence in cases of Addison's disease should be considered of significance. Karakascheff based his conclusions that the cortex was mainly responsible for symptoms of Addison's disease on a study of two cases of atrophy in which the cortex was mainly involved and in which the medulla was normal. Similar cases

led Scott and Oberndorfer to conclude that the cortex is mainly responsible for the symptoms of the disease. Furuta also observed a marked destruction of the cortex without much involvement of the medulla following arteriolar emboli, and concluded that the symptoms were due to destruction of the former. Veit observed a case of thrombosis of the suprarenal vein and believed that symptoms of Addison's disease occurred only when the cortical portion of the suprarenal gland was involved.

Most writers are of the opinion that destruction or impairment of function of both portions is necessary before the complete syndrome is produced, but here again there is no unanimity of opinion as to the relative importance of the two portions. In the production of the symptoms, Falta regarded the low blood pressure, low blood sugar, adynamia and mononucleosis as the result of a lessening of the function of the medulla; the gastro-intestinal symptoms (vomiting, diarrhea), and coma as dependent on the destruction of the cortex. More recently, he concluded that the pigmentation is due to the insufficiency of the medulla. Wiesel,[517] in 1913, altered his former view and stated that asthenia and low blood pressure are the result of an inadequacy of the chromaffin system, whereas the nervous symptoms, the cachexia and lethal end are due to failure of the cortex. Neusser, Löffler and Zondek were in accord with Wiesel's views. Fenwick stated that as the skin changes occur sometimes after, or sometimes before, the onset of the constitutional symptoms, and sometimes not at all, it follows that they cannot be of identical origin. He therefore concluded that the constitutional symptoms are of medullary origin, and that the pigmentary changes are of cortical origin. Fahr and Reiche also believed that pigmentation is due to cortical insufficiency, but they did not state which part is responsible for the other symptoms. They concluded from a study of five cases of primary contracted suprarenal gland in which anatomically the medulla showed little or no change, that functional impairment of the medulla cannot be ruled out. Kovacs, from a study of a case similar to those described by Fahr and Reiche, stated that the symptoms of cortical insufficiency and medullary insufficiency are distinct. He believed, with Omelskyj, that the low blood pressure and the adynamia are due to medullary insufficiency, and that the pigmentation and lethal end are due to cortical insufficiency. Lange, on the other hand, after study of a case with similar pathologic observations, concluded that the adynamia is due to cortical insufficiency.

There are apparently two reasons for these conflicting opinions: (1) too hasty conclusions are reached from the clinical and pathologic observations of a single case of Addison's disease; and (2) experimental evidence offers conflicting views as to the functions of the supra-

renal glands. The extreme variability of symptoms, particularly those of blood pressure and pigmentation, could easily lead one to erroneous conclusions from a study of a single case or a small group of cases. A correlation is made of the outstanding clinical symptoms and the changes in the suprarenal glands of all the available cases in an effort to determine whether or not any relationship exists between the symptoms and the relative degree of destruction of the cortex and the medulla.

It was decided first to determine whether the blood pressure in the cases of primary contracted suprarenal gland differs from that in the cases of tuberculosis of the suprarenal gland, since in the former, the medulla is usually completely destroyed and only small remnants of cortical tissue survive, whereas in the latter, the cortex is the main seat of the involvement and the medulla is usually well preserved.

Relation of Blood Pressure to the Relative Degrees of Destruction of Cortex and Medulla in Suprarenal Tuberculosis and Primary Contracted Suprarenal Gland.—Kovacs, in 1928, and later Omelskyj, concluded from a study of a case of primary contracted suprarenal gland that this condition is to be distinguished from the true form of Addison's disease, as some of the clinical features, principally the fall in blood pressure and the adynamia, are lacking. They decided that these cases should be regarded as representing cortical insufficiency, since the medulla and the extrasuprarenal chromaffin tissue continue to secrete epinephrine despite the structural changes in the cortex, hence, the absence of a drop in blood pressure and the asthenia.

An analysis of the clinical observations in sixty-eight cases of primary contracted suprarenal gland invalidates this view. In Kovacs' cases, on which his view was partly based, there was a systolic blood pressure of 80 mm. of mercury. He stated that the fall in pressure was terminal. He then cited a few instances of Addison's disease in which the blood pressure was within normal limits, and in which the underlying pathologic anatomy was that of primary contracted suprarenal gland. Lange presented a case of Addison's disease in which the pathologic changes were almost identical with those of Kovacs' case, and in which there was a low blood pressure (75 systolic and 45 diastolic) and a marked grade of adynamia. He then concluded that the adynamia was dependent on the destruction of the suprarenal cortex, since the medulla was normal. The evidence on which Lange based his conclusion is fully as justifiable as that on which Kovacs based his conclusions.

An analysis of cases of primary contracted suprarenal gland shows that there are many cases not cited by Kovacs in which repeated examination of the blood pressure showed consistently low readings. Kreibig

reported a systolic blood pressure of 55 mm. of mercury (Riva-Rocci) occurring three months before death. Wahl's patient showed a blood pressure reading of 60 systolic and 42 diastolic five weeks before death. Steinbiss' patient showed a pressure of 70 systolic and 50 diastolic eleven days before death; on the day of death, the systolic pressure dropped to 30. A steady fall of blood pressure over many months was present in case 2, page 762 of the November issue. Kraus reported a case in which the pressure was 70 systolic and 50 diastolic. Certainly, the fall of blood pressure in these cases cannot be regarded as terminal.

A comparison of the blood pressure in cases of suprarenal tuberculosis with that in primary contracted suprarenal gland is made, as in the former, the medulla is mainly involved, and in the latter, the cortex is the main seat of involvement. Among the cases of tuberculosis of the suprarenal glands there are sixty-five in which blood pressure readings are given and among cases of primary contracted suprarenal gland

TABLE 19.—*A Comparison of the Blood Pressure in Suprarenal Tuberculosis with That in Primary Contracted Suprarenal Gland*

Deviations	Systolic Pressure	
	Tuberculosis of the Suprarenal Glands	Primary Contracted Suprarenal Gland
Maximum	155 mm. Hg	135 mm. Hg
Mean	86.55 ± 2.23 mm. Hg	84.08 ± 2.45 mm. Hg
Minimum	30 mm. Hg	55 mm. Hg
Standard deviation	26.73 ± 1.58 mm. Hg	17.47 ± 1.74 mm. Hg

there are twenty-three. The mean, maximum, minimum and standard deviations are as recorded in table 19.

The difference between the means is 2.47, which is less than one time their probable error, so that this difference cannot be considered as significant. Normal and even increased blood pressure is reported as frequently for tuberculosis of the suprarenal glands as for primary contracted suprarenal gland. However, in both groups, the systolic pressure is below normal and about equally decreased.

It is clearly evident, therefore, that the blood pressure is not dependent on the relative degree of destruction of one or the other of the two layers of the suprarenal glands. Normal and even high pressures are observed in cases in which the medulla is totally destroyed, and markedly reduced pressures are seen in cases with normal medulla.

Relation of Symptoms to the Relative Degrees of Destruction of Medulla and Cortex in Primary Contracted Suprarenal Glands.—In an effort to determine further whether the extent of involvement of the medulla, on one hand, and of the cortex, on the other, influences in any way the nature of the symptoms, the cases of primary contracted supra-

renal gland are divided according to the degrees of destruction of the cortex and the medulla. In group 1 are thirty cases in which the cortex is mainly involved and the medulla only slightly involved or normal. In group 2 are nine cases in which both medulla and cortex are about equally involved. In group 3 are four cases in which the medulla is more involved than the cortex. The frequency of the major symptoms (pigmentation, weakness, gastro-intestinal symptoms and changes in blood pressure) are recorded in table 20.

In group 1 (cases in which the cortex is mainly involved; the medulla, slightly involved or normal), marked pigmentation is observed

TABLE 20.—*Frequency of Symptoms with Various Degrees of Destruction of the Cortex and the Medulla*

	Primary Contracted Suprarenal Gland						Tuberculosis of the Suprarenal Glands	
	Group 1*		Group 2†		Group 3‡			
Symptoms	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Pigmentation								
Moderate	12	40.0	5	5.6	2	5.0	17	56.7
Marked	11	36.7	2	2.2	2	5.0	7	23.3
Degree not stated	6	20.0	2	2.2	0	0.0	6	20.0
Absent	1	3.3	0	0.0	0	0.0	0	0.0
Weakness								
Moderate	3	10.0	1	11.1	0	0.0	0	0.0
Marked	15	50.0	5	55.6	3	75.0	16	53.3
Degree not stated	12	40.0	3	33.3	1	25.0	14	46.7
Absent	0	0.0	0	0.0	0	0.0	0	0.0
Blood pressure								
Normal or above	4	13.3	1	11.1	2	50.0	5	16.7
Low	11	36.7	0	0.0	1	25.0	12	40.0
Degree not stated	15	50.0	8	88.9	1	25.0	13	43.3
Gastro-intestinal symptoms								
Present	25	83.3	7	77.8	3	75.0	27	90.0
Absent	0	0.0	0	0.0	0	0.0	0	0.0
Degree not stated	5	26.7	2	22.2	1	25.0	3	10.0

* Thirty cases in which the cortex is mainly involved and the medulla slightly involved or normal.

† Nine cases in which the medulla and the cortex are about equally involved.

‡ Four cases in which the medulla is more involved than the cortex.

in eleven cases; moderate pigmentation, in twelve cases, and no pigmentation, in one case. In group 2 (cases in which the medulla and the cortex are about equally involved), marked pigmentation is present in two cases and moderate pigmentation in five cases. In group 3 (cases in which the medulla is more involved than the cortex) there are two cases of marked pigmentation and two cases of moderate pigmentation of the skin.[1]

1. The reports on the cases in the various groups are referred to in the bibliography under the following numbers: group 1—141, 140, 144 (four cases), 146 (five cases), 149, 151, 152, 153, 155 (cases 1 and 2), 154 (cases 3 and 4), 157, 162, 163, 164 (cases 1 and 2), 167, 168, 171 and case 1 (on page 759 of the November issue); group 2—143, 150, 156, 158, 160 (case 1), 172, 173, 182 and case 2 (on page 762 of the November issue); group 3—142 (cases 1 and 2), 145 and 160.

There is no discernible difference in degree of weakness and degree of digestive disturbance in the three groups. Low blood pressure readings are observed in about equal frequency in the three groups.

Because of the small number of cases in group 3, thirty cases of Addison's disease with tuberculosis of the suprarenal gland were picked at random from the cases collected from the literature and compared with the thirty cases of primary contracted suprarenal gland in group 1.[2] As stated, in the former the medulla, as a rule, is completely destroyed and only small rests of cortical tissue remain, whereas in the latter the cortex is almost completely destroyed and the medulla is normal or only slightly involved. The results are given in column 4 of table 20. Here again, it is seen that the frequency of occurrence of the major symptoms differs but slightly and cannot be considered of any significance.

These cases offer strong evidence to show that the major symptoms of Addison's disease are not dependent on the degree either of cortical or of medullary destruction. All symptoms may be strongly manifested in cases in which the medulla is normal; and there is no apparent difference in the intensity of symptoms in cases in which the medulla is slightly involved or normal and cases in which the medulla is markedly involved.

Experimental Evidence as to the Relative Importance of the Cortex and Medulla.—The opinion that insufficiency of the suprarenal medulla is responsible for the fall of blood pressure is based on the tonus theory of Olliver and Schäfer. Experimental investigation has failed to support this theory.

Biedl found that extraperitoneal removal of the suprarenal glands resulted in a fall in blood pressure that lasted only a few minutes, after which the blood pressure returned to normal and remained so for from two to three days. Later Hoskin and McClure, in ligation experiments on dogs, also failed to observe any significant fall in blood pressure. The results obtained by Gley and Quinguaud in extirpation experiments agree with those of Biedl. The more recent extirpation experiments of Wheeler and Vincent and of Rogoff and Dominquez and the denervation experiments of Stewart and Rogoff furnish strong evidence that the medullary secretion, epinephrine, has little or no effect in maintaining normal blood pressure. In experimental adrenal insufficiency, the fall in pressure is observed only as a terminal symptom and coincides with the onset of marked prostration. The objection is raised by Goldzieher and others that experimental workers have failed to asknowledge the importance of the extrasuprarenal chromaffin tissue, which may

2. Case reports of tuberculosis of the suprarenal glands are referred to in the bibliography under the following numbers: 25, 41, 43, 49, 54, 60, 61, 65, 71, 75, 81, 82, 87, 92, 94, 97, 99, 100, 102, 105 and 127.

act as a compensatory mechanism in the event of the destruction of the suprarenal glands. Although it has been shown by Kohn, Biedl and others that the extrachromaffin tissue secretes epinephrine, it is highly improbable that the quantity secreted is sufficient to exert any influence on the arterial tension (Stewart).

There is little evidence also that reduction in the amount of epinephrine secretion has any effect on the level of the blood sugar. Crowe and Wislocki found little or no change in the carbohydrate metabolism in animals with adrenal insufficiency. In the well controlled experiments of Stewart and Rogoff,[503] experimental hyperglycemia could be obtained in the absence of epinephrine discharge from the adrenal glands, and in animals in which both adrenal glands were removed, a fall in sugar level was not observed until terminal symptoms developed. This is well in accord with the carefully studied cases of Addison's disease of Gyotoku and Momose; Sakaguchi, Kayashi and Katayama, and Lawrence and Rowe. Alimentary hyperglycemia was found to be the same as in normal persons. Sakaguchi, Kayashi and Katayama found no significant lowering of the blood sugar in five cases of Addison's disease and their experimental results are in full accord with those of Stewart and Rogoff. In the cases studied by Lawrence and Rowe, the blood sugar levels are within normal limits. Snell and Rowntree found that hypoglycemia is present in a few cases and only as a terminal phenomenon.

The cause of the gastro-intestinal disturbance is not definitely known. The gastro-intestinal symptoms are often striking in animals suffering from adrenal insufficiency following removal of both adrenal glands. Loss of appetite is one of the earliest signs which usher in the breakdown of the animal (Stewart). Diarrhea is noted only rarely in animals (Hartman). Stewart presented two hypotheses to explain the gastro-intestinal symptoms in animals: (1) that the gastro-intestinal tract shares in the elimination of the poisons that accumulate in the course of adrenal insufficiency and may finally be injured by the poisons; and (2) that the adrenal glands produce a hormone necessary for the continued normal function of the intestinal mucosa. There is little evidence that disturbance of sympathetic tonus is responsible for the gastro-intestinal disorders. Snell and Rowntree stated, "Occasionally gastro-intestinal symptoms are greatly relieved by the administration of epinephrine; perhaps more often the symptoms are not affected or are made worse by its use."

The adynamia frequently seen in Addison's disease is not a prominent symptom in animals suffering from adrenal insufficiency. In chronic adrenal insufficiency in cats, Hartman and Blatz, and in adrenal insufficiency in dogs, Rogoff and Stewart,[493] noted muscular weakness only as

a terminal event. The exact cause of the muscular weakness in man is not understood.

It is agreed by most observers that the lethal end is due to the destruction of the cortex. Biedl found that extirpation of the cortex in mammals is followed by death. Wheeler and Vincent showed that by cauterizing the medulla without removal of the cortex, serious symptoms are not produced; they believed with Biedl that the cortex of the gland is important for life. Biedl found that following complete removal of the interrenal bodies in fishes (*Scyllium* and *Elasmobranchii*) in which the interrenal bodies are separate from the chromaffin organ, death results within a few days. Later Biedl claimed that he was able to remove the cortex in mammals, leaving the medulla intact, and that death followed. The recent work on cortical extracts also supports the view that the cortex is essential for life. Rogoff and Stewart [491] found that cortical extracts prolong the life of adrenalectomized animals, and they also observed beneficial effects when these extracts were administered to patients with Addison's disease. Hartman also claimed to have isolated a substance that prolongs the life of adrenalectomized cats. Koehler claimed to have an extract which had a marked beneficial effect in cases of asthenia, which he attributed to suprarenal insufficiency. It is highly questionable, however, that Koehler was dealing with true cases of suprarenal insufficiency.

In cases of Addison's disease due to tuberculosis, the medulla is early destroyed and in most cases only a small amount of cortical substance remains, which can be detected only microscopically in the later stages of the disease (see page 753 of the November issue). In cases of primary contracted suprarenal gland, large amounts of medullary tissue may remain and yet not prevent a fatal termination.

The disturbance causing the lethal end is not clear. The evidence at hand strongly suggests that death is due to an accumulation of toxic substances. It has been shown by Abelous and Langlois, Biedl and others that the blood of adrenalectomized animals is toxic for other animals. Levin, also, working with decapsulated cats and dogs, obtained a rise of blood pressure in normal animals into which blood from the decapsulated animals had been injected. He suggested that this action is due to the accumulation of harmful substances in the blood stream of the adrenalectomized animals. The nature of this substance is unknown. A relation to the byproducts of muscle metabolism is suggested, as animals that are forced to use muscular exercise following adrenalectomy, succumb more rapidly than adrenalectomized animals that are allowed to rest. It has also been suggested repeatedly that the cortex is capable of neutralizing toxic substances, but proof of the exact nature of this mechanism is still lacking.

It is therefore evident that, following the destruction of the medulla alone, the cortex may function and prevent symptoms of the disease. It is also clear that all symptoms of the disease may be clearly manifest in cases in which the cortex is destroyed and the medulla is intact. However, one cannot assume that an anatomically incomplete medulla functions normally. It has been shown by Stewart that even slight edema of the gland results in a complete inhibition of the secretion of epinephrine. Moreover, there is evidence that for the normal function of the gland, the two parts are essential and act synergistically. Biedl stated that the peculiarity of the vascular supply and the ontogenic and phylogenic development of the suprarenal gland strongly suggest a functional relationship between the two portions. Landau stated that in the development of the gland, the infolding of the cortex suggests a functional relationship between cortex and medulla, as in this way a larger area of the cortex is brought into contact with the medulla. Cramer claimed to have traced a functional relationship between the cortex and the medulla by using stains by which he was able to trace the functional activity of the gland. Hartman and Hartman, using the Folin, Cannon and Denis calorimetric test, the inhibition of intestinal contraction and the denervated iris tests, found that epinephrine is present in the cortex.

It is probable, therefore, that an anatomically intact medulla may not function normally when the cortex is the seat of marked destruction. It is also likely that the extreme variability of symptoms observed in cases of primary contracted suprarenal gland may be due to the varying degree of disturbance in the synergism of the cortex and medulla. However, if this relation is shown not to exist, one must fall back to the theory that the destruction of the cortex alone is responsible for all the symptoms of Addison's disease.

SUMMARY AND CONCLUSIONS

A statistical analysis is made of 566 cases of Addison's disease collected from the literature of the years from 1900 to 1929, inclusive, and from the department of pathology of the University of Minnesota. The following points are emphasized: (1) the etiology and the classification of lesions in the suprarenal glands; (2) the pathologic anatomy of the lesions in the suprarenal glands; (3) the nature and significance of lesions elsewhere in the body, and (4) a correlation between the clinical manifestations of the disease and the changes in the suprarenal glands.

Contrary to the older views, Addison's disease does not occur without lesions in the suprarenal glands. In most cases, both suprarenal glands are destroyed. A few cases of unilateral lesions are recorded. The pathologic changes, in the order of their frequency, are: bilateral

tuberculosis, primary contracted suprarenal gland (atrophy), amyloid disease, neoplasms, vascular lesions, fatty degeneration and pyogenic infections. Syphilis and metastatic tumors of the suprarenal glands are rarely seen in association with Addison's disease. Many other lesions are described, such as pressure atrophy, hypoplasia, trauma, bone marrow metaplasia, etc.

The disease is relatively rare. Both sexes are affected. In the entire series, males are more frequently affected than females. In the cases of primary contracted suprarenal gland, females predominate in the ratio of 1.6 to 1. Heredity can be considered a factor only in rare instances. The age incidence of primary contracted suprarenal gland and that of suprarenal tuberculosis are approximately the same. In the case of tuberculosis of the suprarenal glands, the age incidence follows closely that of deaths from tuberculosis in general.

Tuberculosis of the suprarenal gland is seldom seen in the absence of tuberculous lesions elsewhere in the body. The primary focus is usually in the lung, and ordinarily it is not recognizable clinically. Infection takes place through the blood stream. The medulla appears more susceptible than the cortex to the infection, and it is usually completely destroyed. Remains of the cortex can be made out microscopically in most cases. The disease is progressive and characterized by periods of healing and periods of exacerbation. Healing is rarely observed.

Primary contracted suprarenal gland is a disease of unknown etiology. Two cases are presented which show an early and a late stage of the disease. The pathologic changes indicate that the condition is primarily a slow necrosis involving the cortical cells and leading finally to their disappearance. The inflammatory reaction is secondary to the degenerative changes. The degree of the inflammatory reaction depends on the severity and tempo of the degenerative changes. Partial function is maintained by regeneration in the form of small adenoma-like nodules of cortical cells. There is no evidence that the lesion is due to infection or to the toxic products of lesions elsewhere in the body.

The occurrence of thymic hyperplasia in association with Addison's disease is questionable. As far as could be determined, the weight of the thymus in cases of Addison's disease falls within normal limits.

Changes in other glands of internal secretion are relatively rare. They cannot be considered of importance in the production of the symptoms of Addison's disease.

Anatomic changes in the sympathetic ganglions of the celiac plexus are extremely few and variable in nature. They are not considered of significance in the genesis of the symptoms of Addison's disease.

Gastro-intestinal lesions in Addison's disease are infrequently observed. Peptic ulcers occur in only a few cases. They do not correspond in frequency with those that occur in adrenalectomized animals.

Bilateral tuberculosis of the suprarenal glands without symptoms of Addison's disease is not infrequently seen. These cases have been termed "latent tuberculosis of the suprarenal glands."

Accessory cortical tissue and hyperplasia of the cortex of the suprarenal glands may prevent symptoms of Addison's disease in cases of destructive lesions in the suprarenal glands.

The duration of the disease is not affected by the presence of tuberculosis elsewhere in the body. The duration of the disease in primary contracted suprarenal gland is longer than that in tuberculosis of the suprarenal glands; the mean for the former is 34.02 ± 4.40; for the latter, it is 13.15 ± 2.54 months.

The duration of the disease is significantly longer in cases in which pigmentation is the first and predominant symptom than in those in which pigmentation and weakness occur simultaneously and in those in which the weakness is the initial and prodominant symptom. It is suggested that pigmentation is a mechanism which is compensatory for the destruction of the suprarenal glands.

Conclusions as to the relative importance of the cortex and medulla cannot be drawn from a study of a single case or a small group of cases, as the symptoms of the disease are extremely variable. Evidence is lacking that the symptoms occurring in primary contracted suprarenal glands differ from those occurring in tuberculosis of the suprarenal glands. No appreciable difference in the symptomatology can be noted with varying degrees of destruction of the cortex and medulla. Available experimental and clinical evidence points to the fact that the adynamia, gastro-intestinal symptoms and low blood pressure are due to an accumulation of toxic substances subsequent to suprarenal destruction. The lethal end is due to cortical failure. All symptoms may be present in cases with anatomically normal medulla; however, a functional disturbance of the medulla as the result of disturbance in synergism of the cortex and medulla cannot be denied.

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Notes and News

University News, Appointments, Promotions, Resignations, etc.—Harold Edward MacMahon, London, Ontario, has been appointed professor of pathology and bacteriology in Tufts College Medical and Dental Schools, Boston.

K. Terplan has been appointed pathologist to the Buffalo General Hospital in the place of the late Benjamin Roman.

Annals of Surgery will publish a special number in honor of James Ewing.

In the school of medicine of the University of Texas, Galveston, Texas, Harry L. Klotz has become adjunct professor of pathology.

Waldemar Haffkine, pioneer bacteriologist, born in Odessa of Jewish parents and best known for his inoculations against cholera and plague, has died at the age of 70. He was Pasteur's assistant when he was invited to India, in 1893, to devise methods for the prevention of cholera. The laboratory in which he worked in Bombay is now called the Haffkine Institute. Since 1915 he had lived in Paris.

Beatrice C. Seegal has been made assistant professor of bacteriology in Columbia University.

Eustace L. Benjamin has been appointed assistant professor and Takejiro Matsui research fellow in the department of pathology in the Loyola University School of Medicine, Chicago.

John H. Fisher is now professor of bacteriology in the University of Western Ontario.

Karl Landsteiner, member of the Rockefeller Institute for Medical Research since 1922, has been awarded the Nobel prize in medicine for his discovery of the human blood groups and for his contributions to the study of fundamental problems in relation to immunity. Dr. Landsteiner discovered the human blood grouping about thirty years ago, when he was an assistant in the pathologic-anatomic institute of the University of Vienna, under Anton Weichselbaum.

Alan Gregg has been appointed to succeed the late Richard M. Pearce, Jr., as director for the medical sciences of the Rockefeller Foundation. Dr. Gregg, who will assume his new duties on Jan. 1, 1931, has directed the European work of the Foundation in the medical sciences since 1925.

A New Journal in the Field of Pathology.—Beginning in January, 1931, the American Society of Clinical Pathologists will publish bimonthly the *American Journal of Clinical Pathology* under the editorship of Thomas B. Magath, assisted by an advisory board. The new journal will contain papers on all phases of so-called clinical pathology and related subjects, including technical methods.

Society News.—The Oregon Pathological Society has been organized in Portland, Ore., with Frank R. Menne as president and Warren H. Hunter as secretary.

The next annual meeting of the Federation of American Societies for Experimental Biology will be held in Montreal, Canada, on April 8 to 11, 1931. The secretary is Howard B. Lewis, University of Michigan, Ann Arbor, Mich.

The thirty-first annual meeting of the American Association of Pathologists and Bacteriologists will be held at Western Reserve University, Cleveland, on April 2 and 3, 1931. The special topic will be "Disease of the Liver, Exclusive of Tumors," which is to be presented by F. B. Mallory and G. H. Whipple.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

NORMAL URINE SUGAR IN CYSTOSCOPIC EXAMINATIONS. RUSSELL RICHARDSON and RUTH S. BITTER, Am. J. M. Sc. **180**:171, 1930.

Specimens of normal urine obtained by ureteral catheterization usually show approximately equal amounts of sugar from the two kidneys in the absence of any disease that damages the efficiency of either kidney. When a kidney is badly damaged, the sugar is much decreased compared with that from the normal kidney. An increased secretion of sugar may accompany apparently temporary damage, which is demonstrable by decreased results in phenolsulphonphthalein tests. A slight reduction in functional efficiency may be evident only when the kidneys are forced to excrete sugar at a higher concentration, as following a meal. The damaged kidney cannot excrete urine of as high sugar content as its fellow.

AUTHORS' SUMMARY.

DIABETIC KETOSIS AND FUNCTIONAL RENAL INSUFFICIENCY. A. F. COBURN, Am. J. M. Sc. **180**:178, 1930.

In the alleviation of acute ketosis, urinary excretion of acetone bodies is of perhaps greater importance than their oxidation. It has been repeatedly demonstrated in the group of patients presented that ketonemia may exist in absence of ketonuria. This condition appears at times to precede anuria and should be regarded as a warning to the physician. The development of anuria greatly jeopardizes the recovery of a patient with severe ketosis. Intravenous fluid has been of far greater value in causing excretion of ketone bodies and in correcting anuria than fluid administered by other routes. Recovery from severe ketosis may depend largely on the rapidity with which acetone bodies are excreted by the kidney, and may be prevented by the development of functional renal insufficiency.

AUTHOR'S SUMMARY.

LEUKOPENIA RESEMBLING AGRANULOCYTOSIS WITH RECOVERY. WILLIAM P. THOMPSON, Am. J. M. Sc. **180**:232, 1930.

Seven cases are presented, of an acute, transient, infectious disease associated with high fever, low pulse rate, enlargement of the lymph nodes, leukopenia, relative agranulocytosis, the late appearance of queer whitish spots on the posterior pharyngeal wall and prompt, complete recovery. The etiology is unknown. The cases represent another variant in the group of infections associated with the agranulocytic type of blood picture.

AUTHOR'S SUMMARY.

THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA. W. B. CASTLE, W. C. TOWNSEND and C. W. HEATH, Am. J. M. Sc. **180**:305, 1930.

The active constituent of the gastric contents of the normal human stomach during fasting is in all probability secreted by the mucosa of the stomach and is not detectably present in normal saliva or duodenal contents free from gastric juice, or in the secretions of any portion of the gastro-intestinal tract of the patients with pernicious anemia; this substance is probably organic, thermolabile, possibly enzymic and capable of interaction with protein or closely related substances in neutral solution, resulting in the production of material having, when administered to patients with pernicious anemia, a marked hematopoietic effect.

If an enzyme, it is certainly not pepsin; its properties, as thus far determined, are only in certain respects similar to those of renin. The lack of this particular property of the gastric contents in pernicious anemia is probably the essential defect leading to the development of the disease, through a failure of the normal reaction, occurring in these experiments with beef muscle proteins and normal human gastric juice.

It is also concluded that the existing tests for hydrochloric acid and pepsin of the gastric juice are not necessarily of value in determining the presence or absence of the intrinsic factor essential to the reactions between normal human gastric juice and beef muscle described in these papers.

ABSTRACT OF AUTHORS' SUMMARY.

THE PRODUCTION OF HYPERTROPHIC ARTHRITIS BY INTERFERENCE WITH THE BLOOD SUPPLY. A. D. GOLDHAFT, L. M. WRIGHT and R. PEMBERTON, Am. J. M. Sc. **180**:386, 1930.

Experiments are reported in which the phenomena of arthritis, chiefly of the hypertrophic variety, were brought about in the region of the patella in dogs by ligation of the blood supply to the patella. Control experiments in which an amount of silk ligature equal to that used in the original experiments was placed around the patella, following on an otherwise essentially identical operation, failed to produce any overgrowth after a comparable lapse of time. Analyses of the overgrowth and of the original patella giving rise to the overgrowth show that the percentage of magnesium in the overgrowth was higher than that in the control tissues. The involvement of the mineral metabolism in the region affected is thus clearly indicated. These experiments are in entire consonance with those arrived at, following a different line of reasoning, by Wollenberg, and indicate beyond any reasonable doubt that disturbance of the blood supply must henceforth be regarded as one of the factors capable of producing arthritic change. Taken in conjunction with other work referred to early in the present text, these experiments afford strong evidence that interference with the blood supply, probably in the nature of vasoconstriction, constitutes at least a part, probably a large part, of the underlying physiologic disturbance productive of the phenomena of chronic arthritis, especially the hypertrophic type as encountered in human beings.

AUTHORS' SUMMARY.

PHYSIOLOGIC ACTION OF THE VENOM OF THE HONEYBEE. H. E. ESSEX, J. MARKOWITZ and F. C. MANN, Am. J. Physiol. **94**:209, 1930.

The intravenous injection of the venom of the honey bee, *Apis mellifera*, into dogs and rabbits caused reactions closely resembling those described for rattlesnake venom—a rapid fall of blood pressure, diminution of renal volume, increased volume of the extremities and marked hemolysis with greatly increased volume of the erythrocytes. The skin reaction following its intradermal injection was likewise practically identical with that following injection of rattlesnake venom, and further similarity to this venom and to histamine was shown by maximal contraction of perfused uterus of a virgin guinea-pig and by occlusive bronchial spasm after its intravenous injection into guinea-pigs.

H. E. EGGERS.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS. A. MAURICE WAKEMAN and CLARE A. MORRELL, Arch. Int. Med. **46**:290, 1930.

Determinations of total nonprotein nitrogen and the individual nonprotein nitrogenous components (urea, amino-acid, ammonia, uric acid and creatinine) have been made on the blood of normal monkeys (*Macacus rhesus*) and similar animals with experimental yellow fever. Uric acid, creatinine, rest nitrogen and ammonia are not constantly altered, although in the terminal stages of the

disease, creatinine and rest nitrogen usually rise to a variable extent. The constituents chiefly affected are urea and amino-acids. Amino-acid nitrogen rises rapidly in the terminal stages of the disease; urea nitrogen may rise, but sometimes remains constant or falls. In any case, amino-acid increases proportionately far more, and urea far less, than total nonprotein nitrogen—evidence that the power of the liver to deaminize amino-acids and to produce urea is greatly impaired or destroyed. This functional derangement becomes apparent only during the last hours of life.

AUTHORS' SUMMARY.

FATAL HUMAN ANAPHYLACTIC SHOCK. JESSE G. M. BULLOWA and MENDEL JACOBI, Arch. Int. Med. **46**:306, 1930.

A case of fatal anaphylactic shock after a single injection of diphtheria antitoxin is reported. The pathologic anatomy is described, consisting chiefly of acute pulmonary emphysema, dilatation of the right side of the heart, general venous stasis and visceral congestion; the left side of the heart was contracted and empty. Microscopically, the changes consisted chiefly of thickening of the arteriolar wall, especially in the lungs. These anatomic changes are presented as corroborative morphologic evidence to substantiate the experimental work on the pathogenesis of fatal anaphylactic shock reviewed. This consisted chiefly in overfilling of the lungs, which remained distended, a drop in the peripheral blood pressure with a concomitant rise in the pulmonary arterial pressure, a progressive weakening of cardiac contraction and a slowing and final stopping of the heart, with the right auricle and ventricle in diastole and very much dilated. The cases of anaphylactic shock which came to autopsy are reviewed in detail. Doubt is cast on the rôle of the thymus in such cases.

AUTHORS' SUMMARY.

THE CAUSE OF DEATH FOLLOWING RAPIDLY THE TOTAL LOSS OF PANCREATIC JUICE. R. ELMAN and A. F. HARTMANN, Arch. Surg. **20**:333, 1930.

Using a method that permitted sterile collection of the entire twenty-four hour secretion of the pancreas of the dog, the authors found that death occurred rapidly, generally in about eight days. Examination of the blood revealed rapidly progressive and severe acidosis. This was particularly so in those animals that did not vomit, but if the vomiting was considerable, there was much loss of gastric secretion, and alkalosis supervened. The dogs could be kept alive with daily injections of Ringer's solution. The most important factor in the rapidly fatal outcome was the severe dehydration.

N. ENZER.

THE CAUSE OF DEATH IN UNCOMPLICATED HIGH INTESTINAL OBSTRUCTION. J. C. WHITE and F. A. FENDER, Arch. Surg. **20**:897, 1930.

Complete intestinal obstruction was performed in dogs by severing the small intestine 12 inches (30.48 cm.) below the pylorus. A catheter was placed in the lower segment. The vomitus was collected and injected into the lower bowel, diluted with water. Later, dextrose was added. In spite of the high obstruction, the animals remained in good condition for an entire month. There was, however, loss of weight. The nonprotein nitrogen remained practically stationary, but the blood chlorides revealed a reduction, which developed rather slowly. In the untreated dogs, this reduction would have taken place in from three to five days. The animals were killed after one month. The experiment pointed out that an animal can be kept alive if the loss of secretion from the upper bowel and stomach is prevented by introducing it again into the intestinal circulation. In their conclusion, the authors point out that it is probably unlikely that a toxin formed in the obstructed intestine can be absorbed by the mucous membrane if the blood supply is maintained. The fact that salt solution would neutralize the toxin likewise is disputed, because the animals received no salt from outside sources and still became considerably dechlorinated at the end of the month.

There was a proportionate loss of salts from the tissues corresponding to that from the blood. The nonprotein nitrogen of the blood remained stationary, indicating that there was no destruction of tissue protein. The authors conclude that death in uncomplicated high obstruction is due mainly to loss of salts and water in the gastroduodenal secretions.

N. ENZER.

THE RESPONSE OF PLASMA WATER AND ELECTROLYTES TO ELEVATION OF BODY TEMPERATURE. RUSTIN MCINTOSH, LASLO KAJDI and DOROTHY MEEKER, Bull. Johns Hopkins Hosp. **47**:61, 1930.

By simultaneous determination in rabbits of the volume of the blood and of the plasma and of the concentrations of the total fixed base, chloride and bicarbonate of the serum, it has been possible to study the movement of water and electrolytes into and out of the circulation in response to elevations of the temperature of the body. Fever was produced in a variety of ways—by intraperitoneal injection of two different vaccines, by intravenous injection of a vaccine and by irradiation of the animals with an electric lamp—and with all the methods, an increase in the volume of the circulating blood was brought about, varying only in degree roughly parallel to the change in temperature. Fever caused essentially no constant immediate change in the circulating cell volume; the increase pertained to the plasma fraction. It caused invariably a diminution in the serum concentration of bicarbonate, usually a diminution of the concentration of total base, and sometimes a diminution, but more often an elevation, of serum chloride concentration. The increase in the volume of the plasma, however, represented an influx into the circulation of water and electrolyte of such degree that the total amount of circulating electrolytes was increased over the level existing prior to the elevation of the body temperature. Usually, the total amount of circulating bicarbonate was diminished during fever, but this was not invariably the case. At these times calculations of the composition of the fluid entering the circulation suggested that it was drawn from reservoirs of intercellular fluid, and this hypothesis was strengthened by the vigorous response of one animal in which the store of subcutaneous fluid had been reinforced by hypodermoclysis of normal salt solution. These calculations also suggested that the fluid entering the circulation might at times have a concentration of electrolytes lower than that of normal plasma or of intercellular fluid, which may be offered as a possible explanation of the lowering of the chloride concentration of the plasma often found in pneumonia and other infections. The data obtained afford an approximate estimate of normal standards of total base, chloride and bicarbonate in the circulating plasma of rabbits.

AUTHORS' SUMMARY.

THE OXYGEN RELATIONSHIPS OF UMBILICAL CORD BLOOD AT BIRTH. NICHOLSON J. EASTMAN, Bull. Johns Hopkins Hosp. **47**:21, 1930.

The oxygen relationships of fetal blood, both in utero and at birth, differ widely from those of maternal blood. The principal characteristics of fetal blood in its relation to oxygen are: the high capacity, the low arterial content, the very low venous content and, as a result of these three factors, an extremely high capillary unsaturation. The greatest difference between fetal and maternal blood in relation to oxygen is found in the mean capillary unsaturation, which in fetal blood at birth is three times, and in utero more than twice, that of adult blood. The very high unsaturation of fetal blood in respect to oxygen indicates that the full term fetus in utero exists normally in a state of cyanosis. The evidence suggests that the high oxygen capacity, or hemoglobin content, of fetal blood is an adaptive or "acclimatization" phenomenon due to the low oxygen tension to which the fetal blood in the villous capillaries is subjected, a tension that is estimated as being less than 40 mm. of mercury. Viewed by adult standards, the blood reaching the fetal tissues is low in oxygen, but for the needs of the fetal organism it is evidently adequate.

AUTHOR'S SUMMARY.

RESPONSE OF BLOOD GUANIDINE BASE CONCENTRATION IN NORMAL INDIVIDUALS AND IN PATIENTS WITH LIVER INJURY TO THE INGESTION OF METHYL GUANIDINE SULPHATE. R. McL. ELLSWORTH, Bull. Johns Hopkins Hosp. **47**:106, 1930.

The administration of 200 mg. of methyl guanidine sulphate by mouth did not produce in normal persons a rise of blood guanidine base concentration in four hours. In eight cases of diffuse injury of the liver, the initial blood guanidine base was slightly elevated, and ingestion of the amount of guanidine salt stated produced a conspicuous rise of guanidine in the blood. Observations of blood guanidine base in the manner suggested may prove to be of assistance in detecting injury of the liver.

AUTHOR'S SUMMARY.

DISAPPEARANCE OF DIABETES MELLITUS DURING THE DEVELOPMENT OF CIRRHOSIS OF THE LIVER. JAMES BORDLEY, III, Bull. Johns Hopkins Hosp. **47**:113, 1930.

A case is reported in which severe and long-standing diabetes mellitus cleared up as portal cirrhosis of the liver developed. Attention is called to several similar cases reported in the literature. Cases of this nature are apparently rare, and the experience of others has shown that portal cirrhosis of the liver does not usually exert such an ameliorating effect on diabetes mellitus.

AUTHOR'S SUMMARY.

CORTICAL INSUFFICIENCY OF ADRENALS. OTTO SAPHIR and H. F. BINSWANGER, J. A. M. A. **95**:1007, 1930.

A clinical and pathologic study of two cases of suprarenal cortical insufficiency was made. One case, clinically diagnosed as Addison's disease, showed changes which histologically are similar to the ones found in cytoxic contraction of the suprarenals (Kovacs). An analysis of this case revealed that the blood pressure reached 106 systolic and 78 diastolic, and that the asthenia developed only shortly before the patient died. A possible clinical differentiation between Addison's disease and cortical insufficiency of the suprarenals may be made. The second case, in which death occurred shortly after an appendectomy, showed similar lesions, but much less marked. There were severe degenerative changes throughout regenerated cortical cells. Clinically, the only symptom that could be referred to suprarenal lesions was a diffuse pigmentation of long duration. The sudden death of the patient was attributed to an acute incompetence of the regenerated cortical cells following the operation.

AUTHORS' SUMMARY.

FIXATION OF FOREIGN PROTEIN AT SITE OF INFLAMMATION. VALY MENKIN, J. Exper. Med. **52**:201, 1930.

Foreign protein, such as horse serum, injected into an inflamed peritoneal cavity, penetrates into the blood stream less rapidly than when introduced into the normal cavity. Foreign protein injected into a cutaneous inflammatory area is held in situ for a longer period than when injected into an inflamed peritoneal cavity. Foreign protein introduced into the circulating blood stream accumulates in an inflamed area, where it is found in greater concentration than in normal tissue. Accumulation of foreign protein at the site of inflammation explains the phenomenon of local anaphylaxis described by Auer in rabbits sensitized to horse serum. The antigen accumulating in the inflamed ear reacts with antibody, intensifies a preexisting inflammatory reaction and produces necrosis of the ear.

AUTHOR'S SUMMARY.

THE INFLUENCE OF ULTRA-VIOLET RADIATION ON THE WEIGHT OF ADULT RABBITS, NORMAL AND SYPHILITIC. ALVIN R. HARNES, J. Exper. Med. **52**:253, 1930.

Normal rabbits living in total darkness and exposed to ultraviolet radiation at regular intervals showed a more rapid rate of increase in weight than animals living under the same condition without treatment by ultraviolet rays; but after an initial period of rapid increase, the irradiated animals maintained a lower body weight than those living in the dark. Under the same conditions, animals inoculated with *Spirochaeta pallida* and exposed to ultraviolet light maintained a lower weight than the corresponding control groups living in total darkness. Furthermore, the mortality from pneumonic infection was found to be greater in animals exposed to ultraviolet radiation than in those living entirely in the dark. It is evident, therefore, that, under the conditions given, ultraviolet radiation is detrimental rather than beneficial.

AUTHOR'S SUMMARY.

A-AVITAMINOSIS IN CHICKENS. O. SEIFRIED, J. Exper. Med. **52**:519 and 533, 1930.

The principal tissue changes in the respiratory tract of chickens caused by a vitamin A deficiency in the food are, first, atrophy and degeneration of the epithelium of the lining mucous membrane, as well as of the epithelium of the mucous membrane glands. This process is followed or accompanied by replacement or substitution of the degenerating original epithelium of these parts by a squamous stratified keratinizing epithelium. This newly formed epithelium develops from the primitive columnar epithelium and divides and grows rapidly. The process appears to be one of substitution rather than of metaplasia, and resembles the normal keratinization of the skin or even more closely the incomplete keratinization of the mucous membranes (e. g., the esophagus or certain parts of the tongue of the chicken). In this connection, changes are described which not only afford an interesting insight into the complicated mechanism of keratinization, but also show probable relations between keratinization and the development of Guarnieri's inclusion bodies. Balloon and reticular degeneration of the upper layers of the new stratified epithelium is frequently observed. All parts of the respiratory tract are about equally involved in the process, and the olfactory region as well, so that the sense of smell may be lost. The lesions, which first take place on the surface epithelium and then in the glands, show only minor differences. The protective mechanism inherent in the mucous membranes of the entire respiratory tract is seriously damaged, or even entirely destroyed, by the degeneration of the ciliated cells at the surface and the lack of secretion with bactericidal properties. Secondary infections are frequently found, and nasal discharge and various kinds of inflammatory processes are common, including purulent ones, especially in the upper part of the respiratory tract, communicating sinuses, eyes and trachea. The development of the characteristic histologic process is not dependent on the presence of these infections, since it also takes place in the absence of infection. The specific histologic lesions make it possible to differentiate between A-avitaminosis and some infectious diseases of the respiratory tract.

AUTHOR'S SUMMARY.

THE PLACENTAL TRANSMISSION OF FOREIGN PROTEINS IN RABBITS. FRANCES E. HOLFORD, J. Immunol. **19**:177, 1930.

Horse hemoglobin has not been found to pass the rabbit placenta. Egg albumin, horse or beef serum, the pseudoglobin fraction of beef serum and the globulin fraction of horse serum, injected into pregnant rabbits near term, have, on the other hand, in a number of instances been found to pass the placental barrier in quantity sufficient for demonstration in the serum of the fetus. It is suggested that this fact may be of significance in the further investigation and explanation of certain phenomena of modified resistance in other species, including man, which are likewise supplied with the hemochorialis type of placenta.

AUTHOR'S SUMMARY.

THE INFLUENCE OF CRYPTORCHIDISM AND OF CASTRATION ON BODY-WEIGHT, FAT DEPOSITION, THE SEXUAL AND ENDOCRINE ORGANS OF MALE RATS. V. KORENCHEVSKY, J. Path. & Bact. **33**:607, 1930.

The seminiferous cells secrete hormones that stimulate metabolism and the thyroid gland. Leydig's cells produce hormones that are necessary for the normal growth and development of the adrenals and the hypophysis. Hormones stimulating the sexual organs are produced by both the seminiferous and the Leydig cells. The development of the sexual organs is influenced by the testicular hormones in correlation with (or through) the endocrine glands, namely, the hormones of Leydig's cells with the hypophysis and the adrenals, the hormones of the seminiferous cells with the thyroid. The present data are not sufficient for the elucidation of the possible endocrine function of the Sertoli cells.

AUTHOR'S SUMMARY.

EXPERIMENTAL CRYPTORCHIDISM OF PIGS. V. KORENCHEVSKY, J. Path. & Bact. **33**:683, 1930.

Two domestic pigs were made cryptorchid and compared with two castrated litter mates. The final weight of the cryptorchid pigs was greater than that of the castrated pigs by 13.2 per cent. The amount of retroperitoneal fat, but not that of subcutaneous fat, was slightly increased in cryptorchid pigs. The cryptorchid pigs looked more hairy than the castrates. Histologically, in the cryptorchid testes the seminiferous tissue seemed to have disappeared, the Sertoli's cells were normal, while the hyperplasia of Leydig's cells was greater than in any other species of animals made cryptorchid.

AUTHOR'S SUMMARY.

THE IRRADIATION OF THE BLOOD IN VITRO. ALBERT EIDINOW, J. Path. & Bact. **33**:769, 1930.

The irradiation of the blood in vitro with rays emitted by a quartz mercury vapor lamp (infra-red-2,200 angström units) produces: hemolysis of red corpuscles, destruction of leukocytes, alteration of hemoglobin into methemoglobin, alteration in fibrinogen and tissue kinase, delay of coagulation, and destruction of hemolysins, complement, amboceptors and agglutinins present in the blood serum. The intravenous injection of "irradiated blood" (infra-red-2,200 angstrom units) increases the hemobactericidal power for from one to three hours after injection, and increases the total number of leukocytes per cubic centimeter. The effect is due to the irradiation of the blood corpuscles, since "irradiated serum" and "irradiated lipoids" have no effect. The intravenous injection of washed blood corpuscles sensitized with eosin and exposed to visible rays has a similar action to that of defibrinated blood irradiated with rays shorter than 3,300 angstrom units. The intravenous injection of from 10 to 20 cc. of defibrinated blood intensively irradiated (eighteen hours) is toxic to rabbits and causes death by intravascular clotting. In this respect the action is similar to that of the cytotoxins and other endothelial cell poisons.

AUTHOR'S SUMMARY.

WATER METABOLISM IN SKIN DISEASES. J. K. MAYR, München. med. Wchnschr. **77**:1089, 1930.

Water elimination in dermatitis is of considerable extent, and exudation is shifted from renal to extrarenal. There is only an apparent retention of sodium chloride in pemphigus, because the excretion of salt also is shifted from renal to extrarenal.

AUTHOR'S SUMMARY.

LOCAL TISSUE RESPONSE TO IRRITANTS IN ACUTE DISEASES OF CHILDHOOD. J. BECKER, Ztschr. f. d. ges. exper. Med. **71**:621, 1930.

During the course of various acute diseases in children, blisters were produced in the skin by means of cantharides plasters, and the contents aspirated at intervals

for study. In all cases, the nonspecific reaction in the skin was found to reflect the variations from time to time in the degree of defense preparedness of the organism in general. Observations made during convalescence from pneumonia indicated a marked increase in sensitivity of the defense mechanism, which would explain why even minor infections during that period often cause severe reactions with clinical symptoms. The complications of pneumonia in childhood may be due to an allergic state caused by the increased sensitivity of the defense mechanism.

PEARL ZEEK.

CHOLESTEROL METABOLISM. A. GAÁL, Ztschr. f. d. ges. exper. Med. **71**:690, 1930.

An attempt was made to determine the origin of urinary cholesterol and the rôle of the kidneys in cholesterol metabolism. Cholesterol was not detected in the urine from healthy kidneys even when there was disturbance of cholesterol metabolism in the organism. In many renal diseases, cholesterol was found in the urine, in large quantities in cases of nephrosis, but in small amounts in nephritis and malignant sclerosis. The quantity was not influenced by the alimentary intake of cholesterol. The kidneys appeared to play no active rôle in cholesterol metabolism.

PEARL ZEEK.

BASAL METABOLISM AND THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN DIABETES MELLITUS. A. W. ELMER, L. PTASZEK and M. SCHEPS, Ztschr. f. d. ges. exper. Med. **71**:722, 1930.

In the majority of diabetic patients, the rate of the basal metabolism was found to be normal. An increase of over +20 per cent occurred only in cases complicated by a thyroid toxicosis, and was no key to the severity of the diabetes and could not be attributed to any of the diabetic disturbances. The specific dynamic action of protein was usually normal or subnormal. The administration of insulin had a varying effect on the rate of the basal metabolism, but rarely lowered it. Insulin regularly tended to bring the specific dynamic action of protein toward the normal.

PEARL ZEEK.

KOLPOKERATOSE, A TEST FOR VITAMIN A. W. HOHLWEG and M. DOHRN, Ztschr. f. d. ges. exper. Med. **71**:762, 1930.

When castrated female rats are fed on a diet free from vitamin A, cornified epithelium, called kolpokeratose, appears in the vaginal mucosa, which promptly disappears when vitamin A is added to the diet.

PEARL ZEEK.

FUNCTIONAL TEST OF THE RETICULO-ENDOTHELIAL SYSTEM. Y. TAKEDA, Jap. J. Exper. Med. **8**:399, 1930.

The liver excretion paralleled the disappearance of the dye from the blood stream. No critical disappearance of the dye occurred as claimed by Adler and Reimann.

Pathologic Anatomy

VISUALIZATION OF THE ESOPHAGUS IN THE DIFFERENTIATION OF HEART LESIONS. LEO G. RIGLER, Am. Heart J. **5**:574, 1930.

Four cases are described, with autopsy reports on three of them, in which diagnosis before death was aided by visualizing the esophagus. In mitral disease, the esophagus was compressed by the enlarged left ventricle and displaced posteriorly. In enlargement limited to the right side of the heart, the esophagus was not displaced. In absence of the interauricular septum accompanied by mitral disease, the displacement was much less than with mitral disease alone.

PEARL ZEEK.

LIPOID HISTIOCYTOSIS (NIEMANN'S DISEASE). JAMES M. BATY, Am. J. Dis. Child. **39**:573, 1930.

The sixteenth recorded case of this disease with clinical and pathologic observations is discussed. Outstanding features in this, as in previous cases, were the alterations in the circulating leukocytes and the changes in the central nervous system seen at necropsy. The leukocytes showed striking vacuolization, and many clasmatocytes were present, in the peripheral circulation. The ganglion cells throughout the central nervous system were markedly swollen and vacuolated.

J. N. PATTERSON.

DUBOIS' SEQUESTRA OF THE THYMUS GLAND OF NONSYPHILITIC ORIGIN. E. L. BENJAMIN, Am. J. Dis. Child. **39**:586, 1930.

Most of the Dubois sequestra previously reported were associated with syphilitic changes in other organs, such as osteochondritis, pneumonia alba or interstitial hepatitis. In this instance there were no such changes. In addition, the history did not show any evidences of a syphilitic infection of the mother. She had two normal children, and her Wassermann reaction was negative. The structure of the thymus gland was masked by hemorrhagic extravasation, myelopoiesis, increase in the reticulum cells and the absence of Hassall's corpuscles. Dubois' sequestra, therefore, cannot always be considered as pathognomonic of congenital syphilis. As to the etiology of the thymic sequestra in the present case, an intra-uterine intoxication, possibly associated in some manner with the thyrotoxicosis of the gravid mother, as evidenced by the purpura hemorrhagica, is suggested.

AUTHOR'S SUMMARY.

CHRONIC SUBDURAL HEMATOMA IN INFANTS. DAVID SHERWOOD, Am. J. Dis. Child. **39**:980, 1930.

A comprehensive review of the literature on chronic subdural hematoma, more commonly called pachymeningitis interna hemorrhagica, is presented. The anatomy, pathology and etiology are discussed in detail. Nine cases of this condition are presented, one of which came to autopsy. The diagnosis in the other cases was confirmed by subdural taps. This condition should be thought of in every case in which there are convulsions and enlargement of the head. The prognosis is good if the cyst is drained and if no intercurrent infection takes place. Sequelae occur in a high percentage of cases.

J. N. PATTERSON.

ARTERIOSCLEROSIS IN THE YOUNG DIABETIC PATIENT. H. CLARE SHEPARDSON, Arch. Int. Med. **45**:674, 1930.

A group of fifty diabetic patients who had had the disease for at least five years and who were under 40 years of age was studied to determine the incidence of arteriosclerosis as evidenced by the roentgen ray. The pathogenesis of vascular disease occurring so commonly in diabetes was also investigated. The average age of the entire group was 23.4 years, and the average duration of the disease was 6.9 years. Eighteen cases, or 36 per cent, gave roentgenologic evidence of vascular sclerosis. The data obtained in this investigation are summarized in six tables. Neither the severity of the disease nor the presence of associated pathologic changes, with the possible exception of tuberculosis, can be considered as a pathogenic factor in the development of arteriosclerosis in diabetes. The duration of the disease is important only because the causative factor must act over a reasonable period of time before its effects are manifest. The average values of blood cholesterol found in this group were markedly lower than those heretofore obtained, and, paralleling the reduction of lipemia, the incidence of arteriosclerosis was found to be greatly reduced. The definite lessening of the intensity of the damage resulting from prolonged exposure to diabetes, consequent on the addition of

insulin to diabetic therapy, has resulted in a marked lowering of the average blood lipid content. The parallel reduction in the incidence of arteriosclerosis apparently necessitates the assumption that altered fat metabolism is the morbific factor in the development of vascular disease in association with diabetes mellitus.

AUTHOR'S SUMMARY.

LIPOID NEPHROSIS OF UNUSUAL DURATION. WILHELM EHRICH, Arch. Int. Med. **45**:749, 1930.

A case of genuine lipoid nephrosis has been reported in which the conditions lasted for about seventeen years and showed clinically, as well as anatomically, all the signs of this disease. Several questions concerning lipoid nephrosis have been discussed. As at autopsy the kidneys were still much enlarged, it seems to be doubtful whether true lipoid nephrosis leads to contracted kidneys.

AUTHOR'S SUMMARY.

OCCLUSION OF THE AQUEDUCT OF SYLVIUS. WALTER D. SHELDON, HARRY L. PARKER and JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **23**:1183, 1930.

In two cases, occlusion of the sylvian aqueduct was due to proliferation of the subependymal glia, without increase in nuclear elements, but with increase of the fibrillary portions of the glia; some areas showed edema of the glia around the aqueduct and an apparently normal choroid plexus. Inflammatory phenomena in the brain, ependyma or meninges were absent. The ependymal changes resembled here such as are seen around the central canal of the spinal cord.

In two cases, the occlusion was caused by minute glial tumors (astroblastoma and spongioblastoma), while in two other cases the lesion was not confined to the aqueduct but was widespread, involving remote regions of the brain. Here belong cases of chronic or subacute ependymitis in which the ependyma of the entire ventricular system is affected, including the subependymal tissue. In all the cases studied, an internal hydrocephalus was marked. A clinical diagnosis was not always possible. Even an anatomic diagnosis could be made only after a careful study, for the changes were sometimes minute, while the clinical manifestations were pronounced.

GEORGE B. HASSIN.

INTRACEREBRAL CALCULI. RICHARD C. BUCKLEY, Arch. Neurol. & Psychiat. **23**:1203, 1930.

The patient, aged 44 at the time of death, had been suffering for twenty-three years from periodic attacks of general weakness and inability to walk, mental anxiety, vascular hypertension and epileptic attacks. The latter, numbering from one to five a year, dominated the clinical picture and were preceded by muscular twitchings in the lower part of the left leg. Roentgenograms showed two calculi in the right cerebral hemisphere; ventriculography revealed normal ventricles. Death occurred suddenly, caused, as the necropsy showed, by a hemorrhage (3 cm. in diameter) in the right cerebellar dentate nucleus; one smaller focus was found in the basilar portion of the right side of the pons. The stones were located in the right subcortex, near the walls of the right lateral ventricle, one in the frontoparietal area, just above the corpus callosum, the other near the wall of the occipital horn. The larger stone lay within a cavity the walls of which consisted of connective tissue bordered outside by proliferated astrocytes. The blood vessels, except for two small vessels in the pons, and the meninges, were normal.

The author considers the calculi to have been the result of deposits of lime salts in an old focus of hemorrhage or degeneration; he does not hold them responsible for the clinical manifestations which thus could hardly have been benefited by their removal.

GEORGE B. HASSIN.

ACUTE SACCULATION OF THE UTERUS. W. FLETCHER SHAW, J. Obst. & Gynæc. Brit. Emp. **37**:72, 1930.

Fletcher reports a case of uterine sacculation occurring in the fundus between the fallopian tubes. The patient presented symptoms of three months' pregnancy plus a cystic tumor extending above the uterus to the umbilicus. The sacculated cavity contained the fetus and amniotic waters, and the uterus proper the placenta. Fletcher believes that the sacculation occurs at the point of union of the two Müllerian ducts, which represents a weak spot. Only three other cases of this sort of sacculation are reported in the literature.

A. J. KOBAK.

CHEMICAL STIMULATION OF EPITHELIAL CELLS IN LUNGS. J. S. YOUNG, J. Path. & Bact. **33**:363, 1930.

Active proliferation in the epithelial cells lining the marginal alveoli of the lung of the rabbit can be produced by the intrapleural injection of solutions of various electrolytes. The epithelial reaction is determined almost exclusively by the nature of the cation, the anion playing a negligible part. The alkali metals, lithium, sodium and potassium, and the alkaline earth metals, magnesium, calcium and strontium, are effective only in relatively strong solution, ranging from three-fourths normal to tenth normal; the latter are more potent than the monovalent series. The trivalent metals, aluminum, lanthanum and iron, are more efficient than the bivalent metals of the preceding group, being effective in twentieth normal solution. Higher concentrations of aluminum chloride (e. g., three-twentieths normal) are liable to fail in the production of hyperplasia, owing, it would seem, to the presence of an excess of the reagent. The heavy metals, copper, silver, zinc, cadmium, mercury and lead, relatively weak solution, ranging from hundredth normal to thousandth normal occasion active proliferation. The order of their efficiency — mercury > silver > copper > cadmium > lead > sinc — indicates that a periodic relationship may exist between the biologic properties of the metals and their atomic weights. Generally speaking and subject to certain modifying circumstances, it is suggested that their capacity to produce proliferation is inversely proportional to their solution pressure. Each salt possesses an optimum concentration that seems to be most favorable to the onset of proliferation, and any considerable excess of the reagent is liable to interfere with the progress of the reaction. Certain principles of physical chemistry are enumerated, and it is emphasized that a remarkable parallelism prevails between the several circumstances that regulate the precipitation of negative charged colloids, on the one hand, and the biologic processes of epithelial hyperplasia on the other. It is recalled that the natural adjustment of the hydrogen ion concentration of the tissue fluids in the living animal predisposes the colloids entering into the constitution of the cell membranes to assume a negative charge. The significance of these observations is discussed, and a hypothesis is formulated that a precipitation of the colloids of the cell membrane is an essential phase in the sequence of changes that culminate in cell division.

AUTHOR'S SUMMARY.

ENDOMETRIOMA OF THE CRURAL REGION. LAROYENNE, MARTIN, MICHON and MEYSSONNIER, Gynéc. et obst. **21**:97, 1930

Endometrioma in the crural region is rare. The patient, aged 41, had on the right side a small mass that became painfully enlarged with each menstrual period. At operation, this mass was adherent to the skin and to the femoral and internal saphenous veins. The mass contained typical endometrial-like tissue.

A. J. KOBAK.

VOLVULUS OF UTERINE ADNEXA. LOUIS MICHON, Gynéc. et obst. **21**:103, 1930.

Michon bases his report on a study of five cases, three tubal, two tubo-ovarian and one an ovarian torsion. The tube or adnexal tissue involved showed marked

circulatory disturbance with infarction or accumulation of blood. There was a moderate plastic peritonitis. The tube and ovary on the opposite side were not involved. The resulting pain was dependent less on the degree of torsion than on the extent of the circulatory changes in the affected tissue. A. J. KOBAK.

THE EPITHELIAL CELLS OF THE NEUROHYPOPHYSIS. N. ORLANDI, Arch. ital. di anat. e histol. patol. **1**:1, 1930.

The basophil cells of the posterior lobe of the human hypophysis are described fully on the basis of many observations. These cells are traced to the hypophyseal cleft and the ducts of the pars intermedia, which is regarded as an independent structure.

MALIGNANT LYMPHOGRANULOMATOSIS OF BONES. R. MATZIANI, Arch. ital. di anat. e histol. patol. **1**:31, 1930.

In the case described extensive lesions in the skeleton were due to direct localization and not to extension from adjacent organs.

ANOMALOUS COMMON BILE DUCT. G. FILIPPINI, Arch. ital. di anat. e histol. patol. **1**:97, 1930.

The common duct ended in the pylorus.

MALFORMATION OF LEFT OLFACTORY BULB AND PEDUNCLE. E. E. FRANCO, Arch. ital. di anat. e histol. patol. **1**:105, 1930.

The left bulb and peduncle were replaced by a cyst containing a clear, colorless fluid. The wall of the cyst contained glia tissue.

SARCOSPORIDIOSIS OF THE HEART. G. SCAGLIA, Arch. ital. di anat. e histol. patol. **1**:156, 1930.

In oxen and sheep in the slaughter house at Cagliari, sarcosporidiosis of the heart, especially of the bundle of His, is frequent. Only about fifteen cases of myocardial sarcosporidiosis have been noted in man. From his study of the bundle of His when invaded by *Sarcosporidia* the author concludes that its function depends on its nervous elements.

INFARCTION OF UTERUS. F. LISI, Arch. ital. di anat. e histol. patol. **1**:250, 1930.

In an old marantic woman there was infarction in the posterior wall of the uterus due to thrombosis of the arterial branches.

PERITONEAL ADHESIONS. O. DIEBOLD, Arch. f. klin. Chir. **158**:737, 1930.

Peritoneal adhesions were found in 232 of 700 necropsies. Adhesions become more frequent as age advances, and the incidence is about the same in the sexes. In 106 of the cases with adhesions, no changes were present in the viscera to explain their nature. Of the remaining 126 adhesions, 61 were about the gallbladder, 22 in the lesser pelvis, 20 in the gastric zone, 13 about the appendix and 10 in the duodenal area.

THE EFFECTS OF CHOLESTEROL INTRODUCED INTRAVASCULARLY. G. SEEMANN, Beitr. z. path. Anat. u. z. allg. Path. **83**:705, 1930.

Seemann presents a study of the morphologic changes that resulted from the intravascular injection of colloidal cholesterol. He compares these changes with the generalized lipoidosis that follows the feeding of cholesterol and the localized granuloma that follows the local injection of the substance. The material used was a finely dispersed sol that contained 25 per cent of pure cholesterol. As much as 20 cc. of a 30 per cent dilution of the colloidal preparation could be safely introduced intravascularly, whereas smaller doses of the usual coarsely dispersed

suspension of cholesterol were usually immediately fatal. In acute experiments, three rabbits and two dogs received the material intravenously; in two rabbits the injection was made into the carotid and the femoral artery, respectively, and in one rabbit into the portal vein. In chronic experiments lasting about a month, two rabbits received the cholesterol sol intravenously in repeated doses, the total dosage being 12 and 14 Gm., respectively; four rabbits were fed a mixture of cholesterol and lecithin, and one rabbit received repeated intraperitoneal injections of the colloidal cholesterol. Following intravenous injection, the cholesterol was rapidly removed from the circulation by the capillaries of the lung. In dogs, twenty hours after a single intravenous injection of cholesterol the latter had already largely disappeared from the lungs and was present in the capillaries and bile ducts of the liver and in the kidneys as cholesterol casts. When cholesterol was injected into an artery or portal vein, a slight deposition of the cholesterol was noted in the regional capillaries, but most of the material was again removed by the capillaries of the lung, an observation that the author interprets as evidence of an elective and selective filtration on the part of the capillaries of the lung. Repeated intravenous injections caused marked proliferative reaction on the part of the lung. Capillary emboli of cholesterol led to an obliterating endovasculitis and to proliferation of the septal tissues, resulting in foreign body granulomas containing cholesterol and cholesterol esters. From the lungs, the cholesterol was removed in part by large cells, termed alveolar epithelia, that were free in the pulmonary alveoli. In no instance did the intravascular introduction of cholesterol lead to generalized lipoidosis.

O. T. SCHULTZ.

ALEUKEMIC RETICULOSIS. E. UEHLINGER, Beitr. z. path. Anat. u. z. allg. Path. **83**:719, 1930.

Accepting Aschoff's delimitation of the reticulo-endothelial system, the author presents a case that he interprets as a diffuse hyperplasia of the reticulum cells of that system. The hyperplasia was not associated with any changes in the circulating blood that could be ascribed to the presence in the blood of the proliferated cells. The patient was a man, aged 52, in whose case a diagnosis of tuberculosis of the larynx had been made two years previously. Death occurred two days after his final admission to the hospital and was due to a perforated gastric ulcer and peritonitis. The spleen was enlarged to 1,930 Gm. and the liver to 2,600 Gm. The lymph nodes throughout the body were moderately enlarged. The enlargement of the spleen and lymph nodes was due to hyperplasia of the reticulum cells, which had largely replaced the lymphoid elements of the tissues. A similar condition was present in the bone-marrow. Enlargement of the liver was due in part to fatty change of the liver cells and in part to interlobular aggregations of large polyhedral cells, held to be proliferated Kupffer cells. The author reviews the small number of previously reported cases of reticulo-endothelial hyperplasia. He divides such hyperplasias into two main groups. In one group, termed reticulosis, the proliferating elements are reticulum cells. In the other group, termed endotheliosis or reticulo-endotheliosis, the hyperplasia involves the reticulo-endothelia. The reticuloses are further subdivided into hyperplasias with differentiation of the cells; those in which the proliferated cells exhibit storage of ingested material, those in which the proliferation is the result of stimulation of the protective functions of the cells by infection and those in which the hyperplasia is atypical and may lead to the formation of hematoblastic cells. According to their etiology, the reticuloses are divided into those in which the hyperplasia is due to storage, those in which it is due to infection, the spontaneous hyperplasias, and the dysplastic forms that are to be included among the mesenchymal neoplasms. Reticulum cell hyperplasias that are the result of reaction to infection occur most frequently in childhood. The author's own case and other reported cases lend no support to the view that the monocytes may be derived from the reticulo-endothelial system. In the author's case, in which tuberculosis was also present, the tuberculous process presented an atypical histologic picture in the hyperplastic lymph nodes, in that exudation and caseation were absent.

O. T. SCHULTZ.

EFFECT OF POTASSIUM SALTS ON CELL PROLIFERATION. G. MEYER-DÖRKEN, Beitr. z. path. Anat. u. z. allg. Path. **83**:747, 1930.

The experimental work, carried out under the direction of Leupold, is a continuation of the latter's study (abstr., ARCH. PATH. **9**:924, 1929) of the effects of certain salts and organic compounds on the regeneration of tissue in the healing of wounds. The purpose of the present work was a study of the effect of inorganic salts in promoting local growth of uninjured tissues. A variety of inorganic potassium salts was used in dilutions to 0.00001 per cent and ten millionth molar. In such high dilutions, the salts were probably completely dissociated. Alanine, glycocoll and leucine were used as controls. Each substance was injected in a single dose of 0.5 cc. into the subcutaneous fat between the scapulae of a white mouse. In from four to five days, sometimes seven days, the tissues were removed for histologic study.

The inorganic potassium salts caused proliferation of the endothelia of the tissue spaces of the adipose tissue. The proliferation resulted in the formation of organoid, glandlike structures. The stimulation of growth is held to be the action of an ion and not of a salt, both anions and cations apparently taking part in the effect.

O. T. SCHULTZ.

LYMPHOGRANULOMATOSIS OF THE LUNG. H. WEBER, Beitr. z. path. Anat. u. z. allg. Path. **84**:1, 1930.

Lymphogranulomatosis in which the lung is alone or predominatingly involved is difficult of clinical or gross anatomic diagnosis. It is a rare condition, the few reported cases of which are briefly reviewed by the author. Wohlwill divided pulmonary lymphogranulomatosis into three types: a form in which the involvement begins in a bronchus, spreads along the bronchial tree, surrounds the bronchi by a zone of granulomatous tissue, and simulates bronchogenic carcinoma; a form in which multiple nodules of variable size are scattered throughout the lung parenchyma, the gross appearance being that of metastatic tumor of the lung, and a form in which the lung is invaded by continuity of the process from the lymph nodes of the hilus. Weber presents a clinical, gross anatomic and histologic study of seven cases of Hodgkin's disease with marked involvement of the lung. In three of the cases, the process was limited to the lungs and the immediate lymph nodes; in four cases, the process was generalized, but the lungs were the seat of the most marked change. In one of the cases of the first group, the localization was chiefly peribronchial. In the remainder, multiple lesions of variable size were present throughout the lung. In no case did the process appear to be secondary to involvement of the lymph nodes of the hilus. The author postulates a possible entrance of the causative agent by the respiratory path. An associated pulmonary tuberculosis was present in two cases. In one case, in which no evidence of tuberculosis could be detected, the lung contained two large cavities that communicated with the bronchial system. Weber believes that the cavities resulted from necrosis and softening of lymphogranulomatous tissue. The age of the seven patients whose cases are reported varied from 24 to 73 years, most of the patients being of the third decade. Only two of the patients were women. A correct clinical diagnosis of lymphogranulomatosis was made in only two cases, in one of these on the basis of the histologic examination of a removed superficial lymph node. The usual clinical diagnosis was tuberculosis or neoplasm of the lung. The duration of the disease was from two to eight years, the longest being seven and eight years, respectively, in two patients who had received intensive roentgenotherapy for supposed tumor of the lung. Growth of the tissue in and along the walls of the bronchi leads to marked narrowing of the lumen. In one patient, necrosis of the tissue resulted in a fistulous connection between the esophagus and the trachea. The pulmonary lesions may be surrounded by a zone of desquamative or catarrhal pneumonia like that often associated with tuberculosis of the lung. Intimal lesions of histologically specific tissue, similar to intimal tubercles, suggest the spread of the process by the blood stream. As a rule, the blood vessels of the involved tissue were invaded from without.

O. T. SCHULTZ.

HUMAN HEMOCHROMATOSIS. P. SIEBERT, Beitr. z. path. Anat. u. z. allg. Path. **84**:111, 1930.

Three cases of hemochromatosis are briefly described and discussed. All revealed in striking degree the marked pigmentation of the synovia of the joints described by von Recklinghausen in 1889. Especially emphasized are the pigmentation of the epithelial cells of the hypophysis and the presence in the gallbladder in each of the three cases of small pigment calculi that had a high copper content. In striking contrast to the pigmentation of the epithelia of organs with excretory or secretory function, was the slight pigmentation of the most important of the excretory organs, the kidney. Concerning a possible relationship of copper to the causation of the condition, the author notes that all of his patients came from villages engaged in the wine-producing industry, in which copper salts are widely used.

O. T. SCHULTZ.

THE OBLITERATING ENDARTERITIS OF GANGRENE DUE TO EXPOSURE TO COLD. G. B. GRUBER, Beitr. z. path. Anat. u. z. allg. Path. **84**:155, 1930.

In this publication, as in a previous one, Gruber disagrees with Buerger's conception of the histology of the condition to which the latter has given the name thrombo-angiitis obliterans. The disagreement concerns chiefly two points, the histologically specific character of the vascular lesion and the relation of thrombosis to the lesion. Since the gangrene of Buerger's disease occurs usually in persons of an earlier age than does the gangrene of senile arteriosclerosis, Gruber prefers to term it endarteritis obliterans of younger persons. He believes that the true nature of the arterial lesion is to be learned from a study of the smaller arteries rather than from that of the larger ones, and he believes that a study in younger persons of the terminal arteries of the nongangrenous digits of extremities that have been amputated for gangrene following exposure to cold may throw light on the changes that occur in arteries that have been free from arteriosclerotic change. He presents a report of a histologic study of such vessels. The process is a proliferative inflammatory reaction of the subendothelial tissue that leads to marked thickening of the intima. Thrombosis, if present at all, is a terminal manifestation and never a primary one. The elastic lamella reveals little alteration in the early stages of the vascular lesion. In the later organization of the latter, new elastic fibrils are formed and grow out into the proliferated intimal tissue. Gruber holds the lesion described by him to be a productive endarteritis obliterans, of the kind to which Friedländer gave the name arteriitis obliterans in 1876, and identical with the obliterating endarteritis described by Winiwarter in 1879 in a case belonging to the group now known as Buerger's disease. Neurovascular disharmony in the sense of Ricker may be a factor in the proliferative reaction of the endarteritis due to cold, as it may also be in the racial constitutional peculiarity that seems to be present in Buerger's disease.

O. T. SCHULTZ.

MORPHOLOGY AND PHYSIOLOGY OF THE TERMINAL CIRCULATORY SYSTEM. R. MIDSUNO, Beitr. z. path. Anat. u. z. allg. Path. **84**:183, 1930.

The terminal circulatory system, the largest and most important part of the blood vascular system, consists, in the terminology of Midsuno, of the arteriole, the precapillary, the arterial capillary, the venous capillary, the postcapillary and the venule. His observations, chiefly on the capillary part of this system, were made in the living animal, in the unstained and in the vitally stained condition. For vital staining, trypan blue was used. To study the movement of the circulating blood, intravascular injections of carmine suspensions were made. The tongue of the frog was found to be the most satisfactory object for study. For observation of the circulation of the warm-blooded animal, the mesentery of the rabbit served best. The mesentery of the rat was less useful, and that of the guinea-pig and that of the mouse were unsatisfactory because of the fat contained in the mesentery. The animals were narcotized with ethyl carbonate (urethane). In the

arteriole, the layer of adventitial connective tissue that surrounds the artery becomes thin enough to permit the cellular constituents of the wall to be seen. The precapillary consists of an endothelial wall with a very thin layer of supporting connective tissue. The arterial capillary has no such supporting tissue. The lumen of the venous capillary has a zigzag outline in optical section, due to indentations and elevations of the inner surface of the endothelium. The same kind of lumen is present in the postcapillary, which has a very thin layer of connective tissue about the endothelium. The irregularity of the endothelial surface of the venous capillary and postcapillary is an important factor in the mechanics of the circulation through this part of the system. The venule, like the arteriole, has a distinct but transparent adventitial layer. Direct capillary anastomoses occur in small numbers between artery and vein. These correspond to the derivative canals of Hoyer, but have no structural peculiarities and do not transmit an appreciable part of the blood. In the resting tissue, some of the capillaries are contracted and others are dilated. In either case, they may be filled with blood or only with plasma. The author believes that endothelial cells may lose their connection with the capillary wall and may appear in the circulating blood. Cells closely applied to the outer surface of the capillary endothelium take no part in the movements of the capillary; the identity of such cells with Rouget cells was not investigated by the author. Active movements occur only in the arterial portion of the terminal system, namely, in the arteriole, the precapillary and the arterial capillary. These movements consist of automatic, spontaneous, ameboid movements of the endothelium. The so-called contractility of the capillaries is due to a combination of ameboid movements of the endothelium with swelling of its cells. Epinephrine in proper concentration causes contraction of the arterial portion of the terminal system by evoking the active movements of the endothelium described. The velocity of the blood flow through the terminal system varies from time to time and in different vessels of the same region. The angle at which the branches are given off increases progressively from arteriole to capillary, being often greater than 90 degrees in the latter. This facilitates reflux of blood from the capillaries to the arterioles and causes a to and fro movement of the blood frequently seen in the terminal system. The velocity of the corpuscles in the capillaries varies with each corpuscle. The author is convinced that a stream of pure plasma may occur in the capillaries under physiologic conditions. Under cessation of movement of the blood in the terminal system, the author recognizes stoppage of flow of red and of white cells, stasis of plasma, stasis of platelets and stasis of true red and of white cells. Stoppage of flow of red and of white cells differs from stasis of red and of white cells in that in the former the outlines of the red or of the white corpuscles can be distinctly seen, whereas in stasis the blood within the capillaries has a homogeneous red or white appearance. Stasis was rarely observed under physiologic conditions. The regulatory mechanisms of the terminal circulation consist, according to Midsuno, of the ameboid movements of the endothelium, spindle-shaped dilatations of the arterial capillaries, the derivative capillaries, the distensibility and elasticity of the walls of the vessels, the independent movement of corpuscles and of plasma and the angle at which the capillaries are given off.

O. T. SCHULTZ.

ROENTGEN ANEMIA. C. WEGELIN, Beitr. z. path. Anat. u. z. allg. Path. **84**:299, 1930.

A low grade of anemia with slight leukopenia is not uncommon in workers with roentgen rays. Severe anemia is rare. Wegelin adds a case to three previously reported fatal cases of roentgen ray anemia and nine of radium anemia. The condition occurred in a physician, aged 43, who had been active for ten years as a roentgenologist. Three months before his death, he began to complain of fatigue, palpitation and dyspnea on exertion. Two weeks before death, he had a severe hemorrhage from the nose and was admitted to the hospital. His erythrocyte count was 2,000,000, with a color index of 0.78. The leukocyte count was 1,500,

with a relative lymphocytosis and moderate eosinophilia. Three days before death, the red cell count had dropped to 800,000 and the leukocyte count to 900. The blood at this time contained many nucleated red corpuscles, chiefly megaloblasts. Platelets were few. The anemia was of the secondary aplastic type. The essential postmortem anatomic observation was exhaustion or lack of regenerative activity of the bone-marrow. The testes revealed marked, and the lymphoid tissues slight, atrophy. Hemosiderosis noted in the spleen and bone-marrow was ascribed to damage to the reticulo-endothelial system. The reported cases of radium anemia have shown greater regenerative capacity of the bone-marrow than have the fatal cases of roentgen anemia.

O. T. SCHULTZ.

BLOOD VESSELS IN TUBERCLES. W. PUTSCHAR, Beitr. z. path. Anat. u. z. allg. Path. **84**:321, 1930.

Contrary to the usually accepted view that the tubercle is an avascular lesion, Putschar found newly formed capillaries to be present in a fairly large percentage of the lesions examined histologically by him. They often lie beside giant cells, and he believes that a part at least of the giant cells may be formed from the endothelium of such vessels. Vessels may be present in encapsulated caseous tubercles and may be absent in young cellular lesions. In tuberculous granulation tissue, the vessels may lie next to areas of caseation.

O. T. SCHULTZ.

ANENCEPHALY AND HYPOPLASIA OF THE SUPRARENAL GLANDS. G. B. GRUBER, Beitr. z. path. Anat. u. z. allg. Path. **84**:335, 1930.

The frequent association of anencephaly with hypoplasia of the suprarenal glands led Gruber to make a study of the topography of these glands in a series of anencephalic monsters. The suprarenal glands were found to be hypoplastic in twenty-five of twenty-six examples of anencephaly studied. In the twenty-sixth case the suprarenal glands could not be found. In a case of hemicrania with cerebral hernia, the suprarenal glands were abnormally small. In two examples of occipitocervical craniorachischisis, the suprarenal glands were of normal size. Hypoplasia of these glands were frequently associated with malposition; the left often lay behind the vena cava, and the right had a position more ventral to the kidney than normal. In five of the anencephalic monsters, the cranial and vertebral deformities were associated with ventral abdominal hernia. Abnormality in the size and shape of the abdominal cavity due to the deformity caused by defective vertebral closure is probably a factor in this relatively high incidence of ventral hernia in anencephaly. In the five examples of ventral hernia, the kidneys had a position higher than normal, the upper pole being situated high up under the diaphragm. The diaphragm was closed in each instance, an observation that is not in accord with the theory of Kleine that high position of the kidneys may be a cause of diaphragmatic hernia.

O. T. SCHULTZ.

CONGENITAL ABSENCE OF OVARIES WITH INFANTILISM. R. RÖSSLE and J. WALLART, Beitr. z. path. Anat. u. z. allg. Path. **84**:401, 1930.

Rössle and Wallart precede the detailed presentation of a case of congenital absence of the ovaries with infantilism by a discussion of the criteria that must be met before absence of the ovaries may be accepted as congenital, originating in fetal life. Following Morgagni's first careful description of the condition, many reports appeared in the earlier literature. These cases cannot be accepted because the absence of ovarian tissue was not verified microscopically. With the development of histology, the subject disappeared from the literature. Only during the past decade have there again appeared reports of congenital absence of the ovaries verified by careful microscopic examination. The authors accept as valid only the cases of Olivet, Robert Meyer and Randerath, reported in 1925, the case of Schürmann reported in 1927 and their own case. They also accept Morgagni's case

because of the classic completeness of his description. They leave out of consideration clinical cases of infantilism supposedly due to absence of the ovaries. Their patient was a woman, aged 30 years, whose death was due to a gliosarcoma of the cerebellum. She had ceased to grow at 8 or 9 years of age. Mentally, she had been normal. At necropsy, the body was 133.5 cm. long. The size of the body and the proportions of the body and of the internal organs were those of a girl before puberty. The breasts were not developed, and axillary and public hair was absent. The internal labia were absent, but otherwise the internal and external genitalia were like those of a girl 11 years old, except that the ovaries were absent. Careful microscopic examination of the adnexa, uterus and vagina failed to reveal any ovarian tissue. The rete ovarii was present. This contained well differentiated tubules and others that resembled the tubules of the primitive kidney. With the latter were tubular structures that had the morphology of ducts of the epididymis and others similar to the hydatid of Morgagni. At one point, tubules of primitive renal origin formed an adenomatous nodule, and two areas of misplaced cortical suprarenal tissue were encountered. The authors conclude that theirs is an example of true congenital absence of the ovaries, and that the infantilism was due to this defect. The embryonic period at which the defective development first manifested itself or its cause could not be determined. They consider a disappearance of the primitive sex cells in early fetal life most probable. The fact that the rest of the genital system was normally developed indicates that the development of the rest is not dependent on the ovary; these sexual characters are predetermined in the zygote. The rete ovarii and the rete testis are derivatives of the primitive kidney.

O. T. SCHULTZ.

INFILTRATIVE GROWTH OF PLACENTA WITH RUPTURE OF UTERUS. M. STAEMMLER, Beitr. z. path. Anat. u. z. allg. Path. **84**:460, 1930.

Staemmler asks the question whether infiltrative and destructive tissue growth, such as is characteristic of malignant neoplasms and such as is sometimes seen in nonmalignant form in the downgrowth of epithelium into chronically inflamed connective tissue, is always the expression of an increased and abnormal growth activity of the invading tissue; whether it may not at times be the result of lessened resistance of the tissue into which the infiltrating tissue grows. In answer to this question, he gives a microscopic description of the placenta and uterus of a patient who had spontaneous rupture of the uterus due to invasive growth of the placenta. The patient, who was 32 years old, had had a normal delivery ten years previously. At the end of the second month of the pregnancy that resulted in death, uterine bleeding followed the lifting of a weight. This was controlled, and she was able to resume her work. Toward the end of the fourth month of pregnancy, while at work, she suddenly fell to the floor with intense abdominal pain. Immediate laparotomy revealed a ruptured uterus, with the fetus in the abdominal cavity. Supracervical amputation of the uterus failed to save the life of the patient. In the microscopic examination of the specimen, it was seen that chorionic tissue, in the form of intact villi, of syncytial masses and of masses of cells of the Langhans layer, had invaded and penetrated the uterine wall. The invading chorionic epithelium did not appear malignant. Only where it came in contact with the uterine muscle did it exhibit greater proliferative activity, and here without any change in cell type. The most striking feature, and the one on which Staemmler lays greatest stress in his interpretation, was the absence of any decidual reaction. This characteristic Staemmler's case shares with the others reported in the literature. Also common to all the reported cases of infiltrative growth of the placenta is the fact that the condition has been noted only in multipara, never in primigravida. According to Staemmler, the decidual reaction is the mechanism by which the maternal tissues restrain the histolytic activity of the chorionic epithelium. When this reaction is absent, as it is in placenta destruens, the uterine wall is invaded, not because of increased growth activity of the epithelium, but because of the lessened resistance that the maternal

tissues oppose to the chorionic epithelium. The failure of the normal decidual reaction to occur is not due to absence of the hormone that incites such a reaction in the tissues, since decidual reaction is usually present in some parts of the decidua, although it is absent at the placental site. In Staemmler's case, such a reaction was noted in the endometrial stroma about glands embedded in the uterine muscle and in the subserous tissues Staemmler believed that the failure of the decidual reaction to occur was the result of change in the endometrium.

O. T. SCHULTZ.

EFFECTS OF IRRADIATED AND NONIRRADIATED ERGOSTEROL ON ARTERIES. W. HEUBNER, Beitr. z. path. Anat. u. z. allg. Path. **84**:559, 1930.

A number of investigators have described toxic effects caused by the administration of irradiated ergosterol in large doses to animals, especially rabbits. Among the effects produced is calcification in various organs and particularly in the arteries. It is also known that the feeding of cholesterol causes arterial changes. The question arises whether the effects brought about by irradiated ergosterol are in part effects of sterol, similar to those caused by cholesterol. In comparable feeding experiments, ergosterol, irradiated ergosterol and cholesterol were fed to rabbits of a strain that had previously been found susceptible to the action of irradiated ergosterol. The latter substance caused degenerative changes in the aorta with marked calcification of the lesions. Cholesterol, which was known to be free from ergosterol, caused atherosclerosis of the aorta without calcification. Nonirradiated ergosterol had no effect on the aorta. Some of the pathologic effects of irradiated ergosterol have been described as reversible, in that they disappear after the administration of the material is stopped. The arterial calcification caused by irradiated ergosterol was found by Heubner to be permanent.

O. T. SCHULTZ.

Microbiology and Parasitology

CHRONIC MENINGOCOCCUS SEPTICEMIA. HARRY VESELL and JOSEPH BARSKY, Am. J. M. Sc. **179**:589, 1930.

Chronic meningococcus septicemia (chronic meningococcemia) was first described in 1902. Its rarity is possibly more apparent than real (Marie.) Scant notice given to this condition is in part due to the title "Epidemic Cerebrospinal Meningitis," which tends to direct all concern to the meninges and ordinary form of meningococcus meningitis. Chronic meningococcemia is characterized by a rather sudden onset with headache, intermittent fever, joint symptoms and a typical erythematous skin eruption. There is little prostration and the course is long, lasting from two to three months. The outcome is usually more favorable than in other septicemias. Meningitis is absent in a large number of cases. When it does occur it comes on late in the illness and apparently does not unfavorably influence the outcome. Other complications are considered. Early diagnosis is difficult, especially because the blood culture is frequently sterile until late in the disease. The treatment is with specific serum. A case is reported.

AUTHORS' SUMMARY.

INOCULATION MALARIA: SEXUAL AND ASEXUAL STRAINS. NICHOLAS KOPELOFF, Am. J. M. Sc. **179**:800, 1930.

The malarial course and therapeutic results in 123 patients (88 females and 35 males) inoculated with a sexual strain were identical with those noted in over 350 patients inoculated with an "asexual" strain of malaria. After seven months, the sexual strain of malaria began to lose its capacity to produce gametocytes. During the succeeding nine months, this was found to be much more striking in female than in male patients. Approximately one third of all the female patients

having malarial parasites failed to reveal the presence of any sexual forms of the plasmodium. The sexual strain of malaria becomes biologically adapted to its host on repeated human passage, as evidenced by its increasing failure to produce gametocytes.

AUTHOR'S SUMMARY.

CYTOPLASMIC INCLUSIONS PRODUCED BY THE SUBMAXILLARY VIRUS. E. F. PEARSON, Am. J. Path. **6**:261, 1930.

The cytoplasmic inclusions that are developed in the duct cells of the submaxillary glands of guinea-pigs as a result of the action of the submaxillary virus are formed later than are the nuclear inclusions. They are also more restricted in distribution, having been found only in the ducts of the mucous and serous portions of the submaxillary, occasionally in the acini and in the ducts of the parotid; whereas the intranuclear inclusions may, in addition, be produced in endothelial cells, fibroblasts, smooth muscle cells and mononuclear leukocytes. The cytoplasmic inclusions are spherical or oval structures, which vary in size from a fraction of a micron to from 6 to 8 microns in diameter. In the fully developed state, the average inclusion is about 3 microns in its long axis. The inclusions are made up of many much smaller individual particles which are densely packed together. Like the cytoplasmic inclusions in other virus diseases, these inclusions are characterized by their relative insolubility in ordinary fixatives. They are basophil in reaction and do not contain fat or lipoid in detectable amounts. They are, moreover, indistinguishable from certain cytoplasmic inclusions of rare occurrence in human submaxillary glands.

AUTHOR'S SUMMARY.

MADURA FOOT DUE TO MONOSPORIUM APIOSPERMUM IN A NATIVE AMERICAN. DOUGLAS M. GAY and JAMES B. BIGELOW, Am. J. Path. **6**:325, 1930.

A case of Madura foot due to *Monosporium apiospermum* is reported, and the literature on pathogenic *Monosporia* is reviewed. Although in the United States Madura foot is a rare disease, it should be considered in chronic osteomyelitis of the foot. It is usually easy to find the grains, and their presence is pathognomonic, but the identification of the infecting organism requires microscopic and cultural study. Diagnosis by biopsy is impossible, unless a grain is included in the section, because the lesion is not histologically characteristic. It may be a simple chronic osteomyelitis, or it may resemble tuberculosis or occasionally simulate syphilis. The patient with Madura foot, especially of the yellow-grain variety, should be started on iodine therapy, unless there is some contraindication for the drug, because of the well known response of *Actinomyces* and *Sporotrichum* infections to iodine. Should the organism prove to be some other type, amputation is the only treatment that promises success.

AUTHORS' SUMMARY.

THE CALCIFICATION OF TUBERCLES BY MEANS OF IRRADIATED ERGOSTEROL. TOM DOUGLAS SPIES, Am. J. Path. **6**:337, 1930.

The administration of repeated large doses of activated ergosterol to rabbits suffering from acute tuberculosis causes extensive deposition of calcium salts within the caseous lesions. The administration of a single large dose produces no demonstrable changes. It is suggested that a diet with high content of vitamin D might possibly be useful in some cases of pulmonary tuberculosis.

AUTHOR'S SUMMARY.

TREPONEMATOSIS IN YUCATAN. GEORGE C. SHATTUCK and KENNETH GOODNER, Am. J. Trop. Med. **10**:177, 1930.

Clinical examinations and serologic tests in a series of 271 cases show that among the Maya Indians near Chichen Itzá in Yucatan syphilis is either rare or so exceedingly mild that it fails to produce clinically recognizable lesions or

positive serologic reactions. Syphilis is relatively common among neighboring people of mixed Indian and white blood. No yaws was recognized clinically in Yucatan and, had it been present among the Indians, positive Kahn tests would have been obtained.

AUTHORS' SUMMARY.

THE BACTERIOLOGY OF LYMPHANGITIS ASSOCIATED WITH ELEPHANTOID FEVER IN PORTO RICO. JENARO SUAREZ, Am. J. Trop. Med. **10**:183, 1930.

In a study of sixty cases of lymphangitis associated with elephantoid fever selected by the author as being typical of the disease, bacterial infection was the primary etiologic factor. The micro-organism usually involved was a hemolytic streptococcus. Experience shows that the streptococci are usually found in pure cultures when these are taken directly from the foci of infection, but cultures taken from the subcutaneous tissue are generally negative. Filariasis as a factor in the production of elephantiasis is not as important as was formerly thought.

AUTHOR'S SUMMARY.

HUMAN RABIES AND RABIES VACCINE ENCEPHALOMYELITIS. PETER BASSOE and ROY R. GRINKER, Arch. Neurol. & Psychiat. **23**:1138, 1930.

A woman, aged 48, received the Pasteur treatment, not because she had been bitten by a dog, but because she handled one in which rabies subsequently developed. She received fourteen subcutaneous injections of 2 cc. each. After thirteen injections, which were always followed by considerable local reaction, weakness of the legs developed, followed the next day by complete paralysis, urinary retention, weakness of the upper extremities and slight respiratory, but no deglutitional, difficulties. There was a flaccid paraplegia with the loss of all the tendon, plantar and abdominal reflexes. Sensibility was not impaired. The temperature rose to 103 F., and the leukocyte count was 25,000 on the date of death. The necropsy revealed universal changes in the cord, especially in the cervicodorsal region. The anterior horn cells were two or three times their usual size, with complete chromatolysis; their number was markedly decreased and many appeared as shadows. There was a perivascular infiltration with proliferated adventitial cells, glial cells and lymphocytes, and the vessels were surrounded by areas of demyelinization. In the latter, the axons were broken up and numerous large cells filled with fat were present. The areas bordering on the softening were covered with numerous microglia cells and their transitional forms. Oligodendroglia cells were swollen and many contained mucin. Near the blood vessels, clumps of mucin-like material in grapelike structure were scattered free in the tissue. In general, the changes resembled those described in cowpox encephalitis.

A man, aged 53, was bitten by a sick dog in the right hand. No Pasteur treatment was given. A year later rabies developed, followed by death in four days. Striking changes of inflammatory nature were found in the medulla; in the rest of the central nervous system the changes were slight, but the ganglion cells were swollen and contained Negri bodies. They showed chromatolysis and increase in oligodendroglia cells containing mucin bodies. The areas of demyelinization seen in the previous case, with accumulation of fat, were absent.

GEORGE B. HASSIN.

CHEMICAL STUDIES ON THE TOXIN PRODUCED BY B. PARATYPHOSUS B (AERTRYCKE TYPE). MAUD L. MENTEN and C. G. KING, J. Infect. Dis. **46**:275, 1930.

The toxic fraction precipitated by concentrated acetic acid from a Berkefeld filtrate of B. paratyphosus B (Aertrycke type) and partially purified was free from phosphorus and sulphur and on hydrolysis yielded a carbohydrate. On intravenous injection, this substance caused a hyperglycemia. The fraction precipitated by ammonium sulphate was not hyperglycemic.

AUTHORS' SUMMARY.

VIABILITY OF THE ORGANISM OF ROCKY MOUNTAIN SPOTTED FEVER WHEN FROZEN. ARTHUR G. KING, J. Infect. Dis. **46**:279, 1930.

The organism of Rocky Mountain spotted fever may be kept alive and virulent in well frozen brain tissue for as long as 321 days. For preserving the organism, frozen brain is a superior medium to brain in glycerol in the cold. Ninety per cent of 52 cases were positive in comparison with 65 per cent of cases with glycerol. By combining several infectious brains and using the frozen subdivided parts of the mixture, infectivity may practically be insured. It is possible to keep the strain of Rocky Mountain spotted fever alive in the laboratory by successive transfers of infectious brain frozen over a long period of time.

The infectiousness of blood well frozen for one month was retained in 85 per cent of thirteen cases, with a dosage of 5 cc. After 95 days' freezing, 7.5 cc. of blood proved virulent. The viability of the organism of Rocky Mountain spotted fever, as expressed by the infectiousness of various quantities of blood frozen over various lengths of time, is represented graphically.

AUTHOR'S SUMMARY.

THE INCIDENCE OF BACTERIA IN FOUR HUNDRED TONSIL CULTURES. HERBERT MARSHALL CODE, J. Infect. Dis. **46**:298, 1930.

In 400 tonsillar cultures, staphylococci are the predominating organism. The streptococci follow the pneumococci in predominance, with the hemolytic streptococci the predominant members of the group. Three per cent of the nonhemolytic streptococci recovered are classed as *Streptococcus cardio-arthritidis*.

There appears to be a definite relationship between the type of organism recovered from tonsillar cultures and the age of the patient, streptococci being more common in younger patients (under 11 years of age.).

There is a definite seasonal difference in the organisms recovered from tonsillar cultures: *B. influenzae, B. mucosus-capsulatus* and the diphtheroids all are more prevalent in the spring and *Micrococcus catarrhalis* in the fall.

AUTHOR'S SUMMARY.

FUSOSPIROCHETAL DISEASE OF THE LUNGS PRODUCED WITH CULTURES FROM VINCENT'S ANGINA. DAVID T. SMITH, J. Infect. Dis. **46**:303, 1930.

It seems fair to conclude from these experiments that fusospirochetal disease of the lungs can be caused by the organisms commonly associated with Vincent's angina, and that the pulmonary lesions are probably due to a symbiosis of a spirochete, a fusiform bacillus, a vibrio and a coccus. It is quite possible that any of the spirochetes of the mouth and a number of the cocci may replace the ones actually used in this experimental synthesis.

AUTHOR'S SUMMARY.

MICROBIC DISSOCIATION IN THE ABORTUS-MELITENSIS GROUP: OBSERVATIONS ON THE MUCOID FORM. WAYNE N. PLASTRIDGE and JAMES G. MCALPHINE, J. Infect. Dis. **46**:315, 1930.

The cultural, morphologic, biochemical and serologic characteristics of a new type occurring in the abortus-melitensis group have been described. This has been called the mucoid form. No attempt has been made to classify it as an S or an R type.

AUTHORS' SUMMARY.

BACTERIA OF THE UPPER RESPIRATORY TRACT AND MIDDLE EAR OF ALBINO RATS DEPRIVED OF VITAMIN A. R. G. TURNER, DOROTHY E. ANDERSON and E. R. LOEW, J. Infect. Dis. **46**:328, 1930.

The bacteriologic study of the nasal cavities and middle ear in seventy-nine albino rats is presented for four groups: normal stock rats, vitamin A deficient control animals, rats on vitamin A free ration which developed xerophthalmia and those on a like diet which did not develop the disease. Four types of

organisms pathogenic in rabbits were encountered. These are classified as *Staphylococcus aureus, Bacillus coli, Micrococcus catarrhalis A* and chromogen 6. The last two are gram-negative cocci.

It is apparent that the pyogenic gram-negative cocci, especially chromogen 6, are encountered more frequently in the animals that show the most severe symptoms of vitamin A deficiency. It is believed that these organisms gain a pathogenic hold during the depressed state of their host resulting from vitamin A deficiency.

Evidence is given that cod liver oil protects against bacterial invasion of the nasal cavities and middle ear.

AUTHORS' SUMMARY.

SUSCEPTIBILITY OF MONKEYS, GOATS AND SMALL ANIMALS TO ORAL ADMINISTRATION OF BOTULINUM TOXIN TYPES B, C AND D. J. B. GUNNISON and K. F. MEYER, J. Infect. Dis. **46**:335, 1930.

Macacus rhesus is highly susceptible to the oral administration of botulinum type B toxin. Its susceptibility to the toxin of *Clostridium botulinum type* C β is somewhat lower. It is resistant to large amounts of botulinum C α and D toxins when these are given by mouth, although readily intoxicated when the toxins are injected subcutaneously.

Small laboratory animals have a marked susceptibility to botulinum type B toxin when this is administered by mouth. They are less susceptible to the toxins of types C α, C β and D. The ratio of the lethal dose by injection to the lethal dose by feeding is much higher for type C α, C β and D toxins than for type B toxin.

Goats are extremely susceptible to botulinum type D toxin. Type C β toxin is also fatal when fed to these animals, but it is less active than type D. The oral administration of type B and C α toxins to goats had no effect in the dosages tested (33,000 and 600,000 M.L.D., respectively.

AUTHORS' SUMMARY.

THE IDENTITY OF BACILLUS SUBTILIS. H. J. CONN, J. Infect. Dis. **46**:341, 1930.

On account of recent confusion in the literature as to the identity of *Bacillus subtilis* the writer has looked into the matter and presents three lines of evidence: from cultures obtained from different sources; from a study of the literature, and from a study of hay infusion. It proves that two distinctly different types of bacteria have been going under this name, one a small-spored organism designated in this article the Marburg type, the other an organism with distinctly larger spores, here designated the Michigan type. The latter is the organism studied in a recent paper by M. H. Soule on microbic association. All the evidence gathered by the author, however, points to the Marburg type (the small-spored organism) as the true *Bacillus subtilis.*

AUTHOR'S SUMMARY.

CULTURAL AND SEROLOGIC REACTIONS OF LACTOBACILLI FROM THE MOUTH. BEATRICE HOWITT, J. Infect. Dis. **46**:351, 1930.

Aciduric rods of the *Lactobacillus* group were isolated from the oral cavity of fourteen persons having either paradentitis or a normal condition of the mouth. These organisms showed variations in colony formation and could be placed in several fermentative groups, but there was no correlation between the two. The fermentative reactions with certain strains were subject to change after a long period.

Positive agglutination occurred with strains of the same fermentative type from one host. A certain correlation between the agglutination and fermentation reactions was noticed, although it was not sharply enough defined to distinguish any very definite groups.

Because of the many variations and similar differences in reactions shown by both intestinal and oral aciduric organisms, it does not seem justifiable to separate the two groups.

As suggested by Roos, the term *Lactobacillus acidophilus* should be used to cover a group of biologically related strains variable in their cultural and morphologic characteristics, and not applied to any one specific strain.

AUTHOR'S SUMMARY.

LESIONS PRODUCED IN RABBITS BY LACTOBACILLUS CULTURES. BEATRICE HOWITT and MARTHA VAN METER, J. Infect. Dis. **46**:368, 1930.

Joint lesions were produced in rabbits by intravenous injections of living aciduric organisms of the *Lactobacillus* group of both dental and intestinal origin. An extensive mucopurulent exudate containing numerous polymorphonuclear leukocytes and macrophages, with occasionally a few gram-positive rods, was induced within the joints, usually in those in the shoulders and the hindlegs, less frequently in those in the forelegs and the hips. The cultures showing the highest bacterial counts and having a predominance of the solid disk or Y type of organisms were those giving the most extensive lesions, regardless of the strain or of the source. Positive cultures could be obtained usually one week after the last inoculation from the liver, spleen, kidney, lungs and several of the joints. Cultures of blood from the heart were rarely positive, and then only when the material was removed within a few days after the last injection.

Positive lesions could be more readily induced in the rabbit by the slower method of inoculation over a longer period of time than by the more concentrated, rapid method.

Subcutaneous or intraperitoneal injection of large quantities of the same aciduric strains into the rabbit produced numerous pyogenic nodules at the site of injection or throughout the peritoneal cavity, usually in the greater omentum, on the liver or the capsule of the spleen, on the diaphragm, or on the wall of the bladder. No joint lesions were noticed, nor were they induced by feeding the organisms.

Certain of the oral and intestinal strains of lactobacilli are thus found to possess a pyogenic property.

It may also be asserted, from the evidence given by Holman's review on focal infections and from that portrayed in the present work, that joint lesions in rabbits are more a function of the circulatory system of the invaded host than of any inherent elective localization of the bacteria involved.

AUTHORS' SUMMARY.

AN EPIDEMIC OF COLDS, BRONCHITIS AND PNEUMONIA DUE TO TYPE V PNEUMOCOCCI. M. C. SCHRODER and GEORGIA COOPER, J. Infect. Dis. **46**:384, 1930.

An epidemic of pneumonia, bronchitis and common colds in a children's home is reported. The more interesting observations were: the explosive nature of the epidemic and the short space of time in which it reached its height, fifty-five patients being admitted to the hospital on the seventh day after the first patients were admitted; the extreme infectivity of the organism; the prostration and cyanosis which accompanied the apparently milder cases, and the definite isolation of an infecting organism commonly classified as belonging to group IV of the pneumococcus group, but which in the research laboratory has been definitely determined by one of us to be a member of type V.

AUTHORS' SUMMARY.

THE RESPIRATORY CATALYSTS OF THE DISEASE-PRODUCING BACTERIA. ARTHUR LOCKE and E. R. MAIN, J. Infect. Dis. **46**:393, 1930.

Copper may be an essential constituent of the catalytic principle that orients cellular respiration and synthesis. It appears to be especially required in cells and tissues accustomed to survive periods of oxygen hunger, and may reach its highest concentration in the respiratory substance of the anaerobic and spore-forming bacteria. The production of toxin by the diphtheria bacillus can be

partially inhibited by reducing the concentration of ionic copper available from its culture medium to a level that still supports normal growth. The bacterial toxins may owe their poisonous characters to contents of copper-carrying respiratory substance, well adapted to further the peculiarly aerobic or anaerobic respiratory processes of the bacterial cells in which they have their origin, but intolerable to the cells of the more highly organized, less aerobic or anaerobic plant and animal tissues into which they may diffuse.

AUTHORS' SUMMARY.

THE HEAT RESISTANCE OF THE VIRUS OF POLIOMYELITIS. H. J. SHAUGHNESSY, P. H. HARMON and F. B. GORDON, J. Prev. Med. **4**:149, 1930.

The exact thermal inactivation point of poliomyelitis virus apparently cannot be determined at the present time because there is no accurate method for standardizing the potency of virus preparations. The results reported suggest that, when a small amount (2 cc.) of a virus of moderate potency is used, the thermal inactivation point is low, about 42.5 C. for thirty minutes. On the other hand, in one experiment the temperature necessary to produce inactivation was higher than 50 C. for thirty minutes, due probably to chance variation in the strength of the virus preparation. In other similar experiments, a temperature of 55 C. for all periods of from five to thirty minutes always produced inactivation of the virus. This accords with the results of other investigators. When large amounts of a virus of moderate potency were used, the thermal inactivation was 52.5 C. for thirty minutes. Apparently an increase in the amount of virus injected caused the difference in the effect on monkeys. These results suggest that at temperatures slightly above 40 C. (42.5) the virus is possibly attenuated or, more probably, that part of the virus is destroyed so that a relatively small inoculum becomes ineffective in producing clinical poliomyelitis. Furthermore, as is shown in another paper, virus that is innocuous in a single injection may produce clinical symptoms of poliomyelitis on repeated injections.

AUTHORS' SUMMARY.

A PARATYPHOID-LIKE INFECTION DUE TO MORGAN'S BACILLUS. LEON C. HAVENS and CATHERINE R. MAYFIELD, J. Prev. Med. **4**:179, 1930.

In a series of 49 cases clinically resembling paratyphoid fever, *Bacillus morgani* was isolated from the feces in all cases, from the blood in 6 cases and from the urine in 11. It was the only significant organism in the feces. Agglutinins for the strain recovered from each patient were present in his serum in significant titers (from 1:40 to 1:2,560). In 21 of the 22 cases in which more than 1 specimen was obtained, the titer increased during the course of the attack. Agglutination tests with other organisms invariably gave negative results. Three strains of Morgan's bacillus tested with 537 serums from normal persons and persons with other diseases agglutinated in five instances in a dilution of 1:20. As none of these serums agglutinated any of the strains in higher dilution than 1:20, the high titers observed in our series of cases are apparently the result of a specific reaction. Examination of the feces of 2,798 healthy adults showed *B. morgani* in only 1.2 per cent. All 44 strains from our clinical cases proved virulent for mice, both on intraperitoneal injection and on feeding.

AUTHORS' SUMMARY.

MENINGOCOCCUS MENINGITIS IN DETROIT IN 1928-1929. JOHN F. NORTON and JOHN E. GORDON, J. Prev. Med. **4**:207, 1930.

The present outbreak of meningococcus meningitis in Detroit began in the spring of 1928 and reached its peak in May, 1929. Although a rapid decline in the number of cases occurred during the summer of 1929, the morbidity rate has been considerably above the norm up to the end of 1929.

The total number of cases reported from Jan. 1 to Dec. 31, 1929, was 867 and the number of deaths was 430—a fatality rate of 50 per cent. This percentage is higher than has been observed in most outbreaks since the introduction of modern

methods of treatment (drainage of the spinal canal and treatment with serum. There is no reason to believe that our patients received treatment later than those in other epidemics. It must therefore be concluded either that the strain of meningococcus encountered was of unusual virulence or that the therapeutic serums available were not specific against this strain.

A study of the age, sex and color distribution of cases shows that a high fatality occurred among infants and adults, that sex was of little importance and that the colored population accounted for more than its share of cases.

The distribution of cases in Detroit indicates that congestion of population was a minor factor in the outbreak.

PARATYPHOID, PROTEUS AND RELATED ORGANISMS IN HEALTH AND IN MISCELLANEOUS INTESTINAL DISORDERS OF MAN. JOSEPHINE MCBROOM, J. Prev. Med. **4**:239, 1930.

Fecal specimens were examined from twenty-nine healthy persons and ninety-seven persons ill with a wide variety of intestinal disorders. Paratyphoid organisms were not found in any of the specimens. Proteus bacilli were found in specimens from one of the healthy persons and two of the ill persons. Organisms related to the paratyphoid and proteus bacilli (paracolon, paraproteus and paratyphoid-like) were found frequently in feces from normal persons (41 per cent), from ulcer patients (40 per cent) and from persons with other intestinal disorders of well defined origin (37 per cent). In cases of obscure origin (diarrhea, constipation and bowel distress), these intermediate organisms appeared rarely (in 4.5 per cent of the cases). Green-producing pinpoint colonies, perhaps identical with Bargen's diplococci, were found in 45 per cent of the seventy-six patients examined for these organisms.

AUTHOR'S SUMMARY.

THE VISIBLE EFFECT OF CASTOR-OIL SOAP ON CERTAIN ORGANISMS. R. R. SPENCER, Pub. Health Rep. **45**:1354, 1930.

Sodium ricinoleate, in appropriate amounts, completely clears the bacterial suspensions of certain species in physiologic solution of sodium chloride, rendering such suspensions water clear.

The density of suspensions of certain other bacterial species is increased by appropriate concentrations of sodium ricinoleate.

The density of still other bacterial suspensions is increased at one concentration and decreased at another concentration. The explanation of such changes is not yet apparent.

Certain bacterial species will grow in plain broth containing 1 per cent sodium ricinoleate.

LOCALIZED INFECTION CAUSED BY YEAST-LIKE FUNGI. T. B. JONES, Surg. Gynec. Obst. **50**:972, 1930.

This represents the third case, recorded, of localized or primary blastomycosis of the spine. In a 29 year old man, there was extensive destruction with collapse of the body of the first thoracic vertebra. Yellow foci of softening were present in the inner portion of the second and third thoracic vertebral bodies extending inward, lifting up the dura. Leading externally, along the second rib, from these destroyed bony structures was an irregular ramifying abscess filled with foul smelling grayish-green, semiliquid material, and in which were many eroded large nerve tracts. Due to the fact that the organisms were not numerous, many sections and careful study of the bones were necessary in order to establish a diagnosis. A review of the previous recorded localized infections is given.

RICHARD A. LIFVENDAHL.

THE CULTURE OF TUBERCLE BACILLI FROM THE URINE. T. VON HÚTH and F. LIEBERTHAL, Surg. Gynec. Obst. **50**:985, 1930.

Based on 1,200 cultures of urine for tubercle bacilli on Hohn's egg medium according to the method of Löwenstein-Sumyeski, the conclusion is drawn that this method is more reliable, simpler and more rapid than inoculation of guinea-pigs.

RICHARD A. LIFVENDAHL.

CULTIVATION OF VACCINIA VIRUS. H. B. MAITLAND and A. W. LAING, Brit. J. Exper. Path. **11**:119, 1930.

The technic and the results of experiments on the cultivation of vaccinia virus in medium containing either rabbit kidney or testis are presented. Little virus is necessary to initiate growth and in almost all cases there is an increase of from 10 to 1,000 times or more. The authors conclude: "In view of the regularity with which cultures have been obtained, the potency of culture-virus and the maintenance of its infectivity during storage, its freedom from bacterial contamination, and the small cost entailed, this or a similar method of culture suggests itself as being suitable for the production of 'vaccine' on a larger scale."

J. N. PATTERSON.

EXPERIMENTAL SYPHILIS OF RABBITS. TANI, KAKISHITA, SANADA and INOUE, Zentralbl. f. Bakteriol. **113**:481, 1929.

Syphilitic material from nine untreated patients in the first and second stages of the disease, when injected into rabbits, gave 78 per cent positive results. Mechanical trauma of the testis of the rabbit seemed to have no influence on the development of syphilitic orchitis or on the further course of the syphilis. In young rabbits the incubation period of the local lesion was longer, but its persistence shorter, than in older rabbits. The keratitis appeared later and disappeared earlier, and the symptoms were lighter in the young animals. The greater the injection dose, the shorter was the incubation period of the first lesion; the further course, however, showed no differences. The inguinal and popliteal lymph nodes from nineteen syphilitic rabbits in from the one-hundredth to the three-hundredth day of infection, when injected into new rabbits, gave 47 per cent positive results. Similar lymph nodes taken from syphilitic rabbits that had been treated with neoarsphenamine gave negative results on injection into new rabbits. Lymph nodes from rabbits that had been given injections of syphilitic material and remained symptomless also yielded negative results on subsequent injection into new animals. In studying the localization of spirochetes in various organs of syphilitic rabbits, the injection of testicular emulsions gave the highest percentage of positive results, followed by the spleen and the lymph nodes. No positive results followed the injection of emulsions of brain from syphilitic rabbits.

PAUL R. CANNON.

THE MORPHOLOGY AND GENESIS OF TUBERCULOUS "EARLY INFILTRATION." H. KUDLICH and F. REIMANN, Ztschr. f. Tuberk. **55**:289, 1930.

This paper is a careful and detailed study of the morphology of a so-called "early infiltration." It was observed in a boy, aged 19, who died following an operation for a conglomerated tubercle of the brain. The x-ray picture of the chest sixteen days before death showed a typical infraclavicular lesion with uninvolved apexes without demonstrable excavation. The pathologico-anatomic examination revealed caseous, acinous-nodose, tuberculous foci in the middle and lower thirds of the upper lobe of the right lung, while the upper third of this lobe was free from lesions. All foci were surrounded by nonspecific inflammatory processes which were diagnosed as perifocal infiltrations. The lower lobe of the left lung contained a calcified primary focus the lymphoglandular component of which was found in the draining lymph node. This case, which is apparently the

first complete pathologico-anatomic report on a case of a relatively young so-called "early infiltration," shows that this lesion was a reinfection and that it occurred without previous apical involvement, confirming the clinical and roentgenologic interpretation received in the German literature during recent years.

MAX PINNER.

FILTRABLE VIRUS IN TUBERCULOSIS. J. T. LEUSDEN, Ztschr. f. Tuberk. **55**:437, 1930.

Filtrates were injected into more than forty guinea-pigs. In no case was it possible to ascertain definitely the existence of a filtrable virus.

MAX PINNER.

THE AUTOLYSATE OF SPUTUM. A. HAVAS, Ztschr. f. Tuberk. **56**:39, 1930.

In autolyzing bacilliferous sputum, the tubercle bacilli decreased in number and showed signs of degeneration. The sterilized filtrate of autolyzed sputum exerts an inhibiting action on bacilli, and the morphologic characteristics of the cultures are changed. Bacilli grown on such a medium are considerably less virulent than the unchanged strain.

MAX PINNER.

STREPTOCOCCI FROM SCARLET FEVER. T. AKIYAMA, Jap. J. Exper. Med. **8**:195, 1930.

Only 5 per cent of the strains of streptococci isolated in Japan fermented mannite compared with 16 per cent as reported by Dick. It was possible to increase only slightly the virulence of the organisms by passage through mice. The toxin was without demonstrable effect in animals. Akiyama found that the toxicity of the toxin varied directly with the quantity of bacteria used to produce it, and that the toxicity increased on passage through mice. The toxin and an extract of the streptococci produced similar skin reactions in man. The best therapeutic antiserum was produced by immunization of horses with both the toxin and the bacteria.

THE BACTERIOLOGY OF ACUTE APPENDICITIS. H. HIROSE, Tohoku J. Exper. Med. **15**:524, 1930.

Bacteriologic examination was made of the contents of the appendix and of the peritoneal pus in a large number of cases of appendectomy. Colon bacilli were found in pure culture in the large majority of cases of appendicitis in the acute stages; in addition, the various forms of streptococci and certain bacilli were found also in pure cultures in occasional cases; associations of the different bacteria also occurred in a relatively small number of cases. The results on the whole correspond with the results previously obtained by others.

Immunology

THE COMPARATIVE VALUE OF TOXOID AND OTHER AGENTS IN THE IMMUNIZATION OF THE PRESCHOOL CHILD AGAINST DIPHTHERIA. A. B. SCHWARTZ and F. R. JANNEY, Am. J. Dis. Child. **39**:504, 1930.

A brief review of the literature dealing with the results of immunization against diphtheria is presented. The authors have found that the toxoid method of immunization is far superior to any of the other methods. It is particularly adapted to the preschool child, for it gives a greater percentage of immune persons than does the toxin-antitoxin method, and it avoids serum sensitization. The best age for the toxoid immunization is around 1 year.

J. N. PATTERSON.

THE EFFECTS OF MERCUROCHROME AND MILK PROTEIN UPON ANAPHYLAXIS. LAY MARTIN and JUSTINA H. HILL, Bull. Johns Hopkins Hosp. **46**:232, 1930.

Mercurochrome and milk protein, if given at a certain time before the shocking dose, will protect a definite percentage of animals against anaphylactic death when the amount of antigen injected is about the effective shocking dose.

AUTHORS' SUMMARY.

INTRADERMAL SENSITIZATION OF GUINEA-PIGS. LAY MARTIN and JUSTINA H. HILL, Bull. Johns Hopkins Hosp. **46**:246 and 254, 1930.

Guinea-pigs that have received intradermal injections of emulsions of whole bacteria, both alive and dead (*Pneumococcus* type I, *Streptococcus hemolyticus* and *Staphylococcus aureus* 209) develop skin sensitization to the same antigen in the remarkably short period of forty-eight hours. This is, so far as we have been able to ascertain, the first time this observation has been made. The skin sensitization remained for at least a month, but by that time had diminished. The strongest sensitization was developed about ten days after the primary inoculation.

Those animals that received daily intradermal injections of milk protein were markedly less sensitive to a second injection of bacterial antigen than the controls. Intramuscular injection of milk protein was less effective in inhibiting hypersensitivity to the bacterial antigen.

AUTHORS' SUMMARY.

LOCAL SKIN REACTIVITY TO VARIOUS BACTERIAL FILTRATES. GREGORY SHWARTZMAN, J. Exper. Med. **51**:571, 1930.

The specificity and the nature of the phenomenon of local skin reactivity to various micro-organisms have been studied. It has been shown that the skin preparatory and reacting factors of various biologically and serologically unrelated micro-organisms are able to substitute for each other, provided they have the power of eliciting the phenomenon for themselves. Additional evidence has been brought concerning the antigenic specificity of the factors eliciting the phenomenon. A variety of nonbacterial substances which are able to increase the permeability of capillaries, elicit inflammation and "block" the reticulo-endothelial cells failed to induce the state of local skin reactivity to *B. typhosus* culture filtrate. Nonbacterial protein substances (crystalline egg albumin and normal horse serum) failed to reproduce the phenomenon. It was not possible to obtain passive transfer of the local skin reactivity. Various conditions influencing the potency of the bacterial culture filtrates have been pointed out. The essential nature of the phenomenon has been discussed together with its significance in relationship to disease.

AUTHOR'S SUMMARY.

IMMUNIZATION AGAINST THE PNEUMOCOCCUS. VICTOR ROSS, J. Exper. Med. **51**:585, 1930.

Feeding heat-killed pneumococci grown in milk produces a fair degree of immunity. Feeding acid-killed degraded avirulent organisms produces little protection. Feeding the desiccated, mechanically disrupted organisms creates a high degree of protection. Feeding the Berkefeld filtrate of sodium glycocholate dissolved cells produce a high degree of immunity. A single ingestion of this material equivalent to between 1 and 5 cc. growth is sufficient to protect a rat against from 1,000 to 10,000 fatal doses. Among rats fed the equivalent of 0.1 cc., an occasional one survives. This degree of protection is present forty-eight hours after the feeding, and to a smaller extent exists in occasional animals at the end of twenty-four hours. The treated animals are resistant to subcutaneous as well as intraperitoneal injections. A single ingestion of hydrochloric acid-killed pneumococci equivalent to between 1 and 5 cc. growth also protects within forty-eight hours against from 1,000 to 10,000 fatal doses intraperitoneally injected. Reference is made to results obtained in preliminary experiments with human beings.

AUTHOR'S SUMMARY.

REACTIONS OF RABBITS TO INTRACUTANEOUS INJECTIONS OF PNEUMOCOCCI. LOUIS A. JULIANELLE, J. Exper. Med. **51**:625, 633 and 643, 1930.

A skin reaction elicited by the injection of the pneumococcus "nucleoprotein," or a solution of the cells from which the acid and heat-coagulable proteins have been removed, is described in rabbits which have previously received repeated intracutaneous injections of heat-killed pneumococci. In terms of bacterial specificity, the skin reaction is considered to be not type-specific, but species-specific. A similar skin reaction to the proteins of pneumococcus occurs in rabbits following the repeated administration by the intravenous or intracutaneous route of the heat-killed organisms or their protein derivatives. The skin reaction may occur independently of resistance to infection. The skin reaction appears to be related to the presence of circulating species-specific antibodies.

About two thirds of the rabbits injected intracutaneously with suspensions of heat-killed S or R pneumococci develop an increased eye reactivity. Eye reactions in these animals may be elicited by the instillation of "nucleoprotein," or of a solution of pneumococcus from which the acid precipitable and heat-coagulable proteins have been removed. The eye reactions are not elicited, under the conditions described, by living R cells or the protein-free, type-specific polysaccharides. Rabbits do not develop an increased eye reactivity following intravenous injections of the intact cell. Rabbits do not develop an increased eye reactivity following injections of soluble derivatives of pneumococcus. Experimental infection by pneumococcus may stimulate eye reactivity in rabbits. Eye reactivity occurs in animals actively resistant to infection. Eye reactions are observed more frequently in rabbits which show the secondary reaction.

Rabbits receiving either intracutaneous or intravenous injections of crystalline egg albumin acquire a "skin sensitivity" but not an "eye sensitivity" to the albumin. Rabbits receiving either intracutaneous or intravenous injections of the "nucleoprotein" of pneumococcus acquire a specific "skin sensitivity" to the "nucleoprotein" but not an "eye sensitivity." Rabbits receiving intravenous injections of a suspension of heat-killed pneumococci acquire a "skin hypersensitiveness" but not an "eye hypersensitiveness" to the "nucleoprotein." The skin hypersensitiveness to the respective proteins is associated with the presence of antibodies in the blood and is transferable by the injection of serum from an actively sensitized to a normal rabbit. Rabbits receiving intracutaneous injections of a suspension of heat-killed pneumococci also acquire a "skin hypersensitiveness" to the "nucleoprotein" of the cell, but they may acquire an eye hypersensitiveness as well. Rabbits injected intracutaneously with a suspension of heat-killed pneumococci show a primary and a secondary skin reaction following the first injection. The intensity of the reactions increases with subsequent injections up to the fourth or to the sixth injection. With later injections these reactions change in character and decrease in intensity. These reactions bear no apparent relation to the presence of antibodies in the blood. Rabbits injected intracutaneously with a suspension of heat-killed pneumococci develop "eye hypersensitiveness" which, under the experimental condition, is not transferable from "eye reactive" to normal rabbits. It appears, therefore, that following the injection of heat-killed pneumococci into the skin a special kind of "eye" and "skin hypersensitiveness" develops which is not related to the presence of circulating antibodies and which cannot be transferred from sensitive to normal rabbits.

AUTHOR'S SUMMARIES.

PHAGOCYTOSIS OF THE PNEUMOCOCCUS BY WHOLE HUMAN BLOOD. HUGH K. WARD, J. Exper. Med. **51**:675 and 685, 1930.

The phagocytic titer of whole human blood against the three types of pneumococcus was determined in a number of subjects. The titer varied over a considerable range in different subjects. Contrary to expectation, the titer in early cases of untreated pneumonia was quite high against the infecting organism, pointing to a local rather than a general lowering of resistance in infection with this organism. Sia's work was confirmed, that the specific carbohydrate has a

specific antiphagocytic action on the blood. This action is more marked in the case of type III than in type I.

In vitro phagocytic experiments with human blood, antipneumococcus serum, pneumococcus specific soluble substance and living virulent pneumococci show that there is a definite phagocytic inhibition zone when strong antiserum is used. If the antiserum is further diluted, there is a zone where phagocytosis is effective. If the serum is diluted still more, phagocytosis gradually falls off, as the very dilute antiserum fails to neutralize the specific carbohydrate, which has a specific antiphagocytic action. The inhibition zone is apparently caused by the specific precipitate (formed by the antiserum and the specific carbohydrate) interfering perhaps mechanically, with the ingestion of the pneumococci by the leukocytes. The inhibition zone is better marked with type III than with type I pneumococcus. As the concentration of antiserum in the zone of effective phagocytosis in vitro does not correspond with the concentration of antiserum generally used in vivo in the serum therapy of pneumonia, this question is discussed.

AUTHOR'S SUMMARIES.

THE EFFECT OF THE ROUTE OF IMMUNIZATION ON THE IMMUNITY RESPONSE TO PNEUMOCOCCUS TYPE I. ERNEST G. STILLMAN, J. Exper. Med. **51**:721, 1930.

The serums of 80 per cent of the rabbits intravenously inoculated with fixed amounts of heat-killed pneumococci contained agglutinins and all showed protective antibodies. The serums of 60 per cent of the intraperitoneally inoculated rabbits contained agglutinins and all showed protective antibodies. The serums of 33 per cent of the intramuscularly inoculated rabbits contained agglutinins and 86 per cent also showed protective antibodies. None of the serums of the subcutaneously inoculated rabbits contained agglutinins although protective antibodies were present in 71 per cent. Although there is a close relationship between the presence of agglutinins and protective antibodies in a given immune serum, these do not run parallel.

AUTHOR'S SUMMARY.

ACCUMULATION OF ANTIBODIES IN THE CENTRAL NERVOUS SYSTEM. JULES FREUND, J. Exper. Med. **51**:889, 1930.

Antibodies can be extracted from the brain and spinal cord of rabbits actively or passively immunized with typhoid bacilli. The titers of the antibodies in the extracts of brain and cord depend on the titer of the blood serum. In actively immunized rabbits the following numerical relationships exist between the titers of the serum and of these organ extracts: The ratio of the titer of the serum is to the titers of extract of brain and of the spinal cord about as 100 is to 0.8; the titer of the serum is to the titer of the cerebrospinal fluid as 100 is to 0.3. In passively immunized rabbits the titer of the serum is to the titer of brain and spinal-cord extract as 100 is to 0.7. The antibodies recovered from the brain are not due to the presence of blood in it for perfusion of the brain does not reduce its antibody content appreciably. Antibodies penetrate into the spinal fluid from the blood even in the absence of inflammation of the meninges. When the penetration is completed the following numerical relationship exists between the titer of the serum and that of the cerebrospinal fluid, 100:0.25. The penetration into the cerebrospinal fluid of antibodies injected intravenously proceeds at a slow rate, being completed only several hours after the immune serum has been injected. The penetration of antibodies into the tissue of the brain occurs at a very rapid rate. It is completed within fifteen minutes. It is unlikely that when the immune serum is injected intravenously the antibodies reach the brain tissue by way of the cerebrospinal fluid, for the antibody titer of the cerebrospinal fluid is lower than that of the brain extract, and antibodies penetrate faster into the tissue of the brain than into the cerebrospinal fluid.

AUTHOR'S SUMMARY.

THE TITRATION OF SCARLATINAL ANTITOXIN IN WHITE PIGS. K. ANDO and K. KURAUCHI, J. Immunol. **18**:341, 1930.

The relative merits and limitations of various methods of titrating scarlet fever antitoxin reported by many authors have been described and discussed in brief. A method of titration of scarlatinal antitoxin with white pigs has been described. This method is not only convenient, but also reasonable since (1) the substance that is responsible for the skin reaction of white pigs was proved to be the essential scarlatinal toxin, and (2) this animal does not react to the nucleoprotein contained in the ordinary Dick toxin which may interfere with the results of the skin test method on human beings.

AUTHORS' SUMMARY.

THE MECHANISM OF SPECIFIC AGGLUTINATION AND PRECIPITATION. HARRY EAGLE, J. Immunol. **18**: 393, 1930.

Agglutinating and precipitating antibodies are a specifically altered fraction of the serum globulin. The antigen-antibody complex, whether sensitized red cells, agglutinated bacteria or the precipitate formed by a soluble protein and the corresponding antiserum, contains this antibody globulin, demonstrable chemically, immunologically and by a change in the cataphoretic, flocculating, interfacial and complement-fixing properties of the antigen toward those of the protein with which it has combined. In the case of the cellular antigen, this antibody is present as an invisible film of specificially adsorbed protein, while in the precipitation reaction, it may constitute the bulk of the material formed. In both cases, the originally hydrophil globulin has become water-insoluble (denatured), on combination with antigen. This change in properties is not a phenomenon peculiar to the immune reactions, but is a commonly observed and as yet unexplained property of adsorbed proteins, responsible for their sensitizing effect on otherwise stable colloidal suspensions. It is suggested that in the case of the immune reactions, this denaturation of the antibody globulin is due to the fact that its specificity is determined by hydrophil groups. When these combine with antigen, hydrophobic groups necessarily face the water phase, determining the surface properties of the antigen-antibody complex. But when normal serum protein is adsorbed, since there are no groups with a specific affinity to antigen, the molecules naturally orient themselves at the interface so that the hydrophil groups face the water, and the adsorbed protein acts as a protective film away from its iso-electric point. There are therefore three factors that determine specific flocculation: The hydrophil antigen is covered with a film of immune globulin, denatured by its combination with antigen. In the absence of electrolytes, the charge due to the ionization of this protein suffices to prevent aggregation. Minute concentrations of electrolyte, however, depress this surface charge below the critical value necessary for stability. The resultant aggregation is therefore primarily of the immune globulin surfaces, and only incidentally of the associated antigen. With insufficient immune serum, only a very small portion of the cell surface is covered with antibody globulin; most of the impacts are between hydrophil antigen surfaces, ineffective in producing cohesion. The more immune serum, the greater is the proportion of antigen surface covered with the sensitizing denatured protein, and correspondingly the greater is the proportion of effective impacts. The optimum ion concentration for flocculation is intermediate between that of the original cell and that of the antibody globulin, shifting toward the latter as the degree of sensitization is increased (i. e., more extensive antibody film). At the optimum reaction, ionization, and therefore the surface charge, are minimal; no added electrolytes are necessary to produce aggregation. In more acid or more basic reaction, the surface charge due to the ionization of the adsorbed protein causes a mutual repulsion of the particles; but traces of electrolytes depress this charge and allow the cohesion of the denatured antibody films. The flocculating ion is always the one opposite in charge to the ionized protein, and its flocculating efficiency increases enormously with increasing valence. The further from the iso-electric zone, the greater is

the degree of ionization, and the more electrolytes are necessary to depress the surface charge below the critical value. As will be shown in a forthcoming paper, the kinetics of specific flocculation, the so-called "Danysz" and "zone" phenomena, and the varying proportions of antigen and antibody in the aggregates formed are all in keeping with the theory of specific aggregation as just presented.

AUTHOR'S SUMMARY.

PARENTERAL DENATURIZATION OF FOREIGN PROTEINS. T. H. BOONE and W. H. MANWARING, J. Immunol. **18**:427 and 431, 1930.

The accelerated denaturization of horse proteins in homologously hypersensitive dogs is due to some specific factor, the nonspecific effect of sensitization being an inhibition or exhaustion of the normal, alien-protein denaturization function.

In dogs, india ink blockade reduces the rate of parenteral alien-protein denaturization fully 80 per cent. The capillary endothelium is therefore, presumably, the dominant factor in such denaturization.

AUTHORS' SUMMARIES.

INCIDENCE OF BLOOD GROUPS AMONG THE MAYA INDIANS OF YUCATAN. KENNETH GOODNER, J. Immunol. **18**:433, 1930.

Two hundred and twenty-three pure Mayas and 202 people of mixed Maya and Spanish blood were grouped. A high percentage for the incidence of group O was found, in the case of the Mayas amounting to 97.7 per cent. This points to the racial purity and antiquity of the Maya stock.

AUTHOR'S SUMMARY.

HYPERSENSITIVENESS TO PRODUCTS OF THE DIPHTHERIA BACILLUS. JAMES M. NEILL and others, J. Immunol. **18**:437, 455, 1930.

The hypersensitive man (individual C) previously reported reactive with toxin-containing, and nonreactive with nontoxin-containing, test materials was studied further by a comparison of the hypersensitive reactivity or nonreactivity of the filtrates of highly and of weakly toxicogenic strains of diphtheria bacilli. With a constant test dose (3×10^{-4} cc.) of filtrate, each of the eighteen highly toxicogenic strains produced a moderate to strong immediate skin reaction; in contrast, none of the fourteen weakly toxicogenic strains gave any reaction at all. This sharp demarcation was acceptable proof that the agent of this man's hypersensitive reaction was consistently present in higher concentration in the filtrates of highly toxicogenic, than in the filtrates of weakly toxicogenic, strains. When dealing with complex mixtures like bacterial filtrates, it is difficult to assign hypersensitive reactions to any one particular constituent. However, in the present instance, significance must be attached to the regular association between toxin and the agent of C's hypersensitiveness, particularly because of the biologic assays of the filtrates for their contents of two other diphtheria constituents (the agent of the delayed "pseudo" reaction and the agent of the immediate reaction on individual A). The fact that some of the weakly toxicogenic strains nonreactive with C were just as potent as any of the highly toxicogenic strains in respect to other diphtheria bacterial substances was important, because it showed that the consistent association between the toxin content and the content of the agent of C's reaction was not due simply to a greater concentration of bacterial substance in the toxicogenic filtrates by virtue of more luxuriant growth or of consistently greater autolysis on the part of the toxicogenic strains. While the evidence is of indirect nature, it strongly suggests that diphtheria toxin is the substance involved in the described hypersensitive immediate skin reaction.

Previous evidence indicative that toxin is the substance involved in C's hypersensitiveness was based on the consistent association of high toxin content of test material with high degree of hypersensitive reactivity and of low or no toxin content with weak or no hypersensitive reactivity. The evidence in this paper

was based on the constant association between the antitoxin content of serum and the capacity of the serum to neutralize the hypersensitive agent when the toxin-containing filtrate was incubated with the serum before injection into individual C. Experiments with similar results were obtained with antitoxin-containing serum of horses, rabbits and men. With the rabbit serums, the use of an "antibacterial," as well as an "antitoxic," serum made it possible to show not only that a serum containing antitoxin was able to neutralize the hypersensitive agent, but also that a serum rich in other antidiphtheria antibodies was unable to neutralize it. The most convincing results were obtained with human serums because it was possible by choice from a large number to select for the tests more purely "antitoxic" serums than could be obtained by the laboratory immunization of animals. The selected human serums, although containing no precipitins and no or only traces of "group agglutinin," were able to neutralize the agent of the hypersensitive reaction. Further experiments demonstrated a quantitative relationship between the antitoxin content and the amount of the respective serum required to neutralize the substance hypersensitively reactive with individual C.

AUTHORS' SUMMARIES.

AGGLUTINOGENS OF HUMAN BLOOD. CLARA NIGG, J. Immunol. **19**:1, 1930.

An extra-agglutinin, demonstrated in several normal serums, is described. The extra-agglutinin described was subsequently found to be identical with the extra-agglutinin 1 of Landsteiner and Levine. The hereditary transmission of the extra-agglutinin was apparently established. The occurrence of an agglutinable factor in human blood was demonstrated by means of suitably absorbed antihuman immune serums. The agglutinable factor demonstrated by such immune serums was subsequently shown to be identical with the N factor of Landsteiner and Levine.

AUTHOR'S SUMMARY.

ELIMINATION OF FOREIGN PROTEIN (EGG-WHITE) IN WOMAN'S MILK. HARRY H. DONNALLY, J. Immunol. **19**:15, 1930.

Evidence of the elimination in the breast milk of food proteins ingested by lactating women has been clinical. Stuart's inability to confirm Shannon's experiments and conclusions casts grave doubt on their validity. Walzer's egg absorption work makes it possible to determine when the lactating mother has unaltered egg protein in her blood stream. This constitutes a valuable guide as to the time to collect the breast milk for the study of its egg content. A human antiegg serum, such as serum F, once found, is available for a long time, and offers considerable latitude to the experimenter. Among receptive skins moderate differences in reactivity are found. A specific test of great delicacy for egg-white is offered by the site in a reactive skin sensitized by human antiegg serum of high reagin content. Serum F sites may react to one part of egg-white in ten billion parts of salt solution or breast milk whey. A method for the preparation of concentrated breast milk whey for testing is presented, although its concentration may not be of great importance. The concentrated whey of breast milk obtained after raw egg ingestion, on an empty stomach and without other food, from three of eight women, gave the specific reaction for egg-white greater than the control, in sensitized sites in two normal recipients for each whey. Four recipients were utilized for the tests. By comparison of the skin reactions obtained with the breast milk whey, with those of known dilutions of egg-white, it is estimated that the concentration of egg-white in one of them was one part in a million, and in each of the others one part of egg-white in a billion parts. An unsuccessful attempt was made to sensitize a guinea-pig passively to egg-white with 2.5 cc. of serum F intraperitoneally, as shown by the uterine strip method of Dale.

AUTHOR'S SUMMARY.

CERTAIN CHARACTERISTICS OF THE INFECTIOUS PROCESSES IN CONNECTION WITH THE INFLUENCE EXERTED ON THE IMMUNITY RESPONSE. L. DIENES and E. W. SCHOENHEIT, J. Immunol. **19**:41, 1930.

The observations described in this paper inform us concerning important properties of the lesions, with the help of which the production of the tuberculin type of sensitiveness is successful. Twenty-four hours after the injection of a large dose of the R1 strain into the testicle, the injection of egg-white in the same place produces tuberculin type of sensitiveness. When intraperitoneal injections are used, forty-eight hour intervals were necessary between the two injections. In the production of the sensitiveness the local reaction at the site of the tubercle bacillus injection played the preponderant rôle because only the injection of egg-white in this place was effective. The intravenous injection of small doses is without effect. At the stage when we injected the egg-white an acute inflammatory reaction is present, with large accumulation of leukocytes around the injected bacteria. The typical tissue reaction of tuberculosis is not yet developed. The latter is not a prerequisite of the development of the tuberculin type of sensitiveness. It was possible to produce a tuberculin type of sensitiveness with the injection of egg-white into the testicle of guinea-pigs infected with smallpox vaccine. With extensive acute inflammatory processes produced with infusorial earth, tapioca and turpentine, the immunity response of the animals was not influenced. The local reactions produced with the antigenic lipoid substances of the tubercle bacilli also remained without effect. With the soluble substances of the tubercle bacillus we did not succeed in increasing the antigen response. Different considerations make it improbable that the substances of the bacterium are directly responsible for the influence exerted by the lesions on the immunity response. We give also a review of unsuccessful experiments in which we tried to transfer passively the increased response toward the antigens with the products of tuberculous lesions.

AUTHORS' SUMMARY.

ALLERGIC REACTIONS IN VACCINIA-IMMUNE RABBITS. RICHARD THOMPSON, J. IMMUNOL. **19**:63, 1930.

Evidence is given to indicate that allergic reactions do occur in a certain percentage of vaccinia-immune rabbits. Some evidence is given indicating that the reactions obtained may be partly due to homologous testicle tissue reacting with organ-specific antibodies. That the virus does play some part in the reaction is indicated by the fact that the reactions are much greater in virus-immune animals than in animals immune only to testicle tissue. While a state of hyperimmunity tends to reduce the amount of induration in the allergic reaction, there is no conclusive evidence that the negative results in some animals are due to this hyperimmunity. The chief factor determining the occurrence or nonoccurrence of an allergic reaction is the individual factor in the animal. From apparently successful passive transfer — general and local — of the allergic state and from the apparent acceleration of vaccinal reactions by treatment with immune serum, it seems probable that the allergic reactions are the result of antigen-antibody reactions. Evidence in a human subject of a local factor in the allergic reaction indicates that the antigen-antibody reaction concerned does not entirely depend on antibodies in the serum.

AUTHOR'S SUMMARY.

RESISTANCE OF GUINEA PIGS VACCINATED WITH BACILLUS CALMETTE-GUERIN (B C G). S. A. PETROFF and W. STEENKEN, JR., J. Immunol. **19**:79, 1930.

Animals vaccinated intraperitoneally or subcutaneously with living B C G developed some degree of protection. Guinea-pigs vaccinated by feeding showed no allergy up to four weeks, nor any perceptible immunity. These studies confirm Langer's observations that the resistance established with B C G is not greater than that established with heat-killed bacilli.

AUTHORS' SUMMARY.

A Quantitative Complement-Fixation Technic. Harry Eagle, J. Infect. Dis. **46**:231, 1930.

To a series of tubes containing arbitrary, but constant, quantities of complement and the known reagent are added increasing amounts of the unknown. After one-half hour at 37 C., sensitized cells are added, and the residual complement determined from the time required for complete hemolysis as described in the text. The amount of antibody (or antigen) present in the unknown can then be expressed on any arbitrary scale; the unit being taken as the amount necessary to fix 75 per cent of complement in the presence of an arbitrarily fixed quantity of antigen (or antibody). Although it can be used in any type of fixation (by bacteria, red cells or specific precipitate), the method is particularly valuable in the Wassermann reaction, making possible an accurate titration of syphilitic reagin, and allowing a definite evaluation of the so-called "anticomplementary" and "doubtful" reactions, in terms of positive and negative.

Antigens for the Precipitation Test for Syphilis. Emil Weiss, J. Infect. Dis. **46**:285, 1930.

An optimal antigen has been devised, which offers the following advantages: It is equally useful in the Wassermann, the Kahn and the author's test; its preparation is simple and every step is well defined; it has a much wider specific zone than the antigens recommended by Kahn, and it does not require additional sensitizing or correcting.

Author's Summary.

Agglutination of Typhoid Bacilli in Serums of Patients Having Unrelated Infections. Ruth Gilbert and Marion B. Coleman, J. Infect. Dis. **46**:311, 1930.

The observations are, of course, too limited to furnish a basis for sweeping conclusions. It is evident, nevertheless, that the results of the agglutination reaction with typhoid bacilli must be interpreted in the light of clinical manifestations or of bacteriologic observations, since it has been shown that agglutination may be encountered in specimens collected from patients during febrile diseases other than typhoid fever, even though the patients have never received typhoid vaccine nor to their knowledge had typhoid fever, and that a fluctuation of the agglutination titer, considered by some as definite evidence of typhoid fever, may occur in cases in which this infection is definitely excluded.

Authors' Summary.

Syphilitic Antigen Derived from Blood Serum. R. L. Kahn, A. M. Malloy and M. Nishio, J. Infect. Dis. **46**:413, 1930.

Both syphilitic and nonsyphilitic serums contain lipoids that possess specific precipitinogen properties. By extraction of serums with ether and subsequent taking up of the lipoids in alcohol, an antigen is obtained in alcoholic solution that can be employed in the Kahn reaction.

Powdered beef serum, when subjected to extractions with ether and subsequently with alcohol, yields an antigen possessing a sensitivity similar to that of Kahn standard antigen prepared from powdered beef heart.

Lipoids extracted from syphilitic serum act as precipitinogens when mixed with the same serum in vitro.

Authors' Summary.

Relation Between Concentration of Lipoids in an Antigen and Its Sensitiveness in the Precipitation Reaction with Syphilitic Serum Globulins. M. Nishio, J. Infect. Dis. **46**:420, 1930.

An attempt was made to find whether in the precipitation reaction for syphilis the quantitative relation between the concentration of lipoids in an antigen and its sensitiveness with syphilitic serum would hold true if the serum globulins were

substituted for the serum. Antigens of varying lipoid concentrations were prepared and precipitation tests made with serums and serum globulins according to the Kahn technic. The globulin solutions gave somewhat more sensitive reactions than the unfractioned serums. The zone of maximum sensitiveness was the same with serums as with serum globulins. This zone corresponded to a given (optimum) concentration of antigenic lipoids. An increase or decrease in lipoids beyond this concentration resulted in antigens of lesser sensitiveness.

AUTHOR'S SUMMARY.

BRUCELLA ABORTUS AGGLUTININS IN PORCINE BLOOD. R. A. BOAK and C. M. CARPENTER, J. Infect. Dis. **46**:425, 1930.

Agglutination tests for *Brucella abortus* agglutinins on 4,014 serums from samples of porcine blood collected in New York State and from seven midwestern states showed 64, or 1.54 per cent, to be positive.

The percentage of agglutination for 1,054 samples from New York State was 0.19, while 1.89 per cent of 2,735 samples from Ohio, Illinois, Indiana and Missouri were positive.

AUTHORS' SUMMARY.

OPTIMUM QUANTITATIVE RELATION BETWEEN ANTIGEN AND SERUM IN PRECIPITATION REACTION IN SYPHILIS. M. NISHIO and E. B. MCDERMOTT, J. Infect. Dis. **46**:435, 1930.

For maximum precipitation with a given antigen, whether "standard" or "sensitized," it is necessary to employ optimum proportions of serum and antigen suspension. A 12:1 proportion of serum to standard antigen suspension and a 6:1 proportion of serum to sensitized antigen suspension were found to be the most sensitive. An excessive amount of antigen suspension over serum and to a lesser degree of serum over antigen suspension tended to inhibit precipitation. The precipitation zones with the two antigens are similar but not identical, sensitized antigen giving a wider precipitation zone than standard antigen. Relatively excessive amounts of the former antigen are capable of giving more sensitive reactions than similar amounts of standard antigen. When the serum amounts are excessive in relation to the antigen amounts, somewhat more sensitiveness is shown with the standard antigen.

Globulin solutions from syphilitic serums react in approximately the same proportions with standard and sensitized antigen suspensions as the unfractioned serums, except that with the former somewhat more sensitive reactions are obtained.

Positively reacting nonsyphilitic rabbit serums, when used in varying proportions with standard and sensitized antigen suspensions, show precipitation zones similar to those shown by human syphilitic serums.

AUTHORS' SUMMARY.

THE MICROSCOPIC AGGLUTINATION TEST IN PNEUMONIA. ALBERT B. SABIN, J. Infect. Dis. **46**:469, 1930.

A method of microscopic agglutination is described in which the organisms are smeared with the serum on a slide, allowed to dry rapidly and stained.

By the method described, the type of infecting pneumococcus can be determined in two ways: (*a*) with the patient's sputum, usually within from three to four hours after its injection into the mouse; (*b*) with several drops of the patient's blood, by determining the type of agglutinins that are neutralized after the administration of polyvalent serum. This procedure is applicable to a limited number of patients; it is especially indicated in cases in which sputum is not obtainable and it is desired to know whether the infecting pneumococcus is of a type for which antiserum is available.

The microscopic agglutinin test on a single drop of the patient's blood can be used to demonstrate the presence or absence of active infection, as indicated by the neutralization of homologous agglutinins in the circulation, as well as the active production of antibody, and may thus be used as a guide in controlling the dosage of antipneumococcus serum.

AUTHOR'S SUMMARY.

THE RELATION OF HEMOLYSINS AND TOXINS IN DIPHTHERIA CULTURES ISOLATED FROM ACUTE CASES. RALPH H. HEEREN and EMERSON MEGRAIL, J. Infect. Dis. **46**:485, 1930.

Correlation between hemolytic properties and toxicogenicity is not sufficiently marked to make it a reliable laboratory test for the toxicogenicity of *Corynebacterium diphtheriae*.

The property of hemolysis in diphtheria bacilli is transient, generally disappearing as the length of time the cultures have been on laboratory mediums increases.

A formerly hemolytic organism may be made to regain hemolytic powers by a series of passages through laboratory animals, but the ability is soon lost when cultures are once more transferred to laboratory mediums.

For a considerable period, growth on blood agar has little tendency to increase hemolysins.

Variations are shown in the susceptibility of the blood of laboratory animals to hemolysis. The rabbit's blood offers greater resistance to hemolysis and the blood of different animals is less uniform than that of the guinea-pig.

Hemolysis is a factor apart from toxicogenicity and also is not definitely correlated with virulence.

AUTHORS' SUMMARY.

THE EFFECT OF IRRADIATION ON COBRA VENOM AND ANTIVENIN. ALBERT EIDINOW, Brit. J. Exper. Path. **11**:65, 1930.

As a result of irradiation of cobra venom and antivenin it was shown that the neurotoxin present in a solution of cobra venom in saline solution was destroyed only by rays shorter than 2,800 angstrom units unless sensitized with eosin. The photodynamic action of eosin is arrested by the presence of blood and serum. Hemolysins and cytolysins were destroyed by rays longer than 2,800 A. U., but not by rays longer than 3,300 A. U. Antivenin is resistant to prolonged irradiation as obtained in serum.

AUTHOR'S SUMMARY.

THE ANAPHYLACTIC REACTION OF THE ISOLATED UTERUS OF THE RAT. C. H. KELLAWAY, Brit. J. Exper. Path. **11**:72, 1930.

Experiments indicate that the results of sensitization, as judged by the reaction of the isolated smooth muscle, are very irregular with active sensitization and are extremely regular with passive sensitization. It is shown that the anaphylactic reaction of the muscle is one of contraction and not of relaxation, and that this is due to the interaction between the precipitating antibody, fixed in the plain muscle, and the specific anaphylactic antigen. The production of symptoms, either in the actively or in the passively sensitized animals, by large intravenous injection of the antigen (crystalline hen-egg albumin) is an infrequent event.

J. N. PATTERSON.

A STUDY OF VACCINAL IMMUNITY IN RABBITS BY MEANS OF IN VITRO METHODS. S. R. DOUGLAS and WILSON SMITH, Brit. J. Exper. Path. **11**:96, 1930.

The white cells of normal blood were shown to take up vaccinia virus in vitro. Normal whole blood possesses some degree of viricidal power, which is largely dependent on a thermolabile constituent of the serum. Different anticoagulants have different effects on the viricidal activity of the blood. Heparin is shown to be a suitable anticoagulant for in vitro experiments of the type recorded. The blood, spleen and testis of an immune rabbit show far greater viricidal power than those of a normal rabbit. Evidence is put forward suggesting that the increase of viricidal power by immunization depends on (1) alterations of the tissue cells themselves — cellular immunity — and (2) an opsonic or perhaps a stimulin action of some of the serum constituents — humoral immunity.

AUTHORS' SUMMARY.

THE TUBERCULOSIS IMMUNIZATION (B C G) AT LÜBECK. L. LANGE, Klin. Wchnschr. **9**:1105, 1930.

This report contains the results of Lang's investigation of the immunization with B C G at Lübeck, during which seventy-four children received injections, seventeen of which died from acute generalized tuberculosis. The bodies of fifteen of those who died were examined. Lange pleads against a hasty condemnation of the B C G immunization.

EDWIN F. HIRSCH.

ACTIVITY OF THE RETICULO-ENDOTHELIAL SYSTEM IN ANAPHYLACTIC SHOCK. MARCEL HAENDEL, Ztschr. f. d. ges. exper. Med. **71**:675, 1930.

A series of guinea-pigs was sensitized to horse serum. After an interval of time (from twenty to twenty-five days), various substances were given, preceding the reinjection of a lethal shock dose of horse serum. The reticulo-endothelial system was inactivated and shock prevented by the use of each of the following: peptone, heterologous serum, milk, bacillary emulsion, epinephrine, calcium, experimental acidosis, glycerin, neoarsphenamine, merbaphen, barbituric acid, alcohol, ether and atropine. Other substances stimulated the reticulo-endothelial system and facilitated shock: insulin, thyroiodin, potassium, pantopon, cholereticum ataphanyl and physostigmine. The effects of experimental alkalosis, hypertonic dextrose solution, hypophysin and ovarin were not clear.

PEARL ZEEK.

PEPTONE SHOCK AND THE RETICULO-ENDOTHELIAL SYSTEM. MARCEL HAENDEL and J. MALET, Ztschr. f. d. ges. exper. Med. **71**:683, 1930.

When the reticulo-endothelial system of guinea-pigs is blocked with india ink, the administration of peptone does not cause shock as in untreated animals, but produces prostration and loss of appetite, with hyperemia of the lungs, liver and spleen.

PEARL ZEEK.

Tumors

PAPILLOMAS OF THE CHOROID PLEXUS. W. P. VAN WAGENEN, Arch. Surg. **20**:199, 1930.

The author reports two cases of true papilloma of the choroid plexus, both in the left ventricle. The method of demonstrating blepharoplasts was employed as a method of differentiating between ependymal papillomas and papillomas of the choroid plexus. In both cases reported here blepharoplasts could not be demonstrated. Likewise, no glial fibers were present in either tumor. There is evidence in the literature and in one of the cases reported here that this tumor may be seeded by the cerebrospinal fluid into the brain tissue, where it reproduces itself in a papillary formation. The implantations were well away from the original tumor. The distinguishing feature of such plexus tumors is their benign histologic nature and lack of invasive properties. The two cases are reported in detail, and there is a summary of the forty-five cases reported in the literature. A curious point discovered in the literature was that 93 per cent of these tumors were in the left lateral ventricle.

N. ENZER.

MULTIPLE MALIGNANT ADENOMAS OF THE KIDNEY. E. S. JUDD and J. P. GRIER, Arch. Surg. **20**:240, 1930.

The kidney of a man, aged 46, was removed at operation. It contained numerous tumor nodules and was about five times normal size. The cut surface showed five distinct grayish-red tumors varying in size up to 12 cm. in diameter. These were surrounded by a small amount of normal-appearing kidney tissue. Microscopically these tumors were not encapsulated, but adjoined normal kidney tissue. There

was some evidence of compression of the tubules and glomeruli. The histology was that of an adenoma, with large polygonal cells. This case is the nineteenth to be reported.

N. ENZER.

CHRONIC CYSTIC MASTITIS. J. S. RODMAN and H. INGLEBY, Arch. Surg. **20**:515, 1930.

Great stress is placed on the importance of appreciating the normal phases of activity of the tissue of the breast and the importance of differentiating these from pathologic changes. Any tumor that does not change with local treatment after one menstrual period should be removed, and if the frozen section does not definitely establish a benign process, the lesion should be treated as carcinoma. The senior author has changed his point of view from one held many years ago on the relationship between this disease and carcinoma. Formerly, he considered chronic cystic mastitis as definitely precancerous, but at the present time he believes that this disease is a result of the interference of the normal physiologic processes in the breast, and cannot be considered definitely as precancerous.

N. ENZER.

THE INDUCTION OF TUMORS WITH CARBON DIOXIDE SNOW. I. BERENBLUM, Brit. J. Exper. Path. **11**:208, 1930.

Experiments on mice with two carcinogenic agents, tar and carbon dioxide snow, are reported. It is shown that when the two agents are applied concurrently, the induction of tumors is inhibited, but when either is applied after the other a summation of effect is obtained. It is generally held that a carcinogenic agent is ineffective if the intensity of irritation is insufficient. The present experiments suggest that it may also be ineffective if the intensity of irritation is too great. They also suggest that there is an optimum intensity of irritation for effective carcinogenesis.

ALFRED M. GLAZER.

ROUS SARCOMA NO. 1: INFLUENCE OF MODE OF EXTRACTION ON THE POTENCY OF FILTRATES. W. E. GYE and W. J. PURDY, Brit. J. Exper. Path. **11**:211, 1930.

There is a rough correspondence between the structure of each example of the Rous sarcoma no. 1 and its degree of filtrability. There is a rough correspondence between the potency of an extract and the amount of precipitable protein that it contains; but some specimens yield extracts that are very highly potent, although they contain no protein detectable when tested by boiling and addition of acetic acid. Extraction with strong salt and subsequent dilution to physiologic strength gives more highly potent extracts than does direct extraction with physiologic solution of sodium chloride. By the saturated-salt method some examples of the Rous sarcoma no. 1 which once would have been classed as nonfiltrable are now found to be filtrable. Since it is shown that in practice the classification is dependent on the efficiency of the technical tests employed, added point is given to the question of whether the strict separation of tumors into filtrable and nonfiltrable groups is not entirely artificial.

AUTHORS' SUMMARY.

Medicolegal Pathology

CINCHOPHEN POISONING. L. J. STACY and F. R. VANZANT, Minnesota Med. **13**:327, 1930.

A woman, aged 52, took cinchophen daily for some six weeks, discontinuing its use because of nausea and vomiting. A week later intense jaundice appeared, and death took place sixteen days after she became jaundiced. The liver weighed only 903 Gm. and presented the typical appearances of acute yellow atrophy.

FRACTURE OF THE SECOND CERVICAL VERTEBRA. H. DÜRCK, Beitr. z. path. Anat. u. z. allg. Path. **84**:353, 1930.

Fracture of the second cervical vertebra alone is rarely encountered. Two kinds of fracture are described, one involving the odontoid process, the other the lamina, the latter being the rarer of the two. Dürck describes in considerable detail an example of each kind. The case of fracture of the odontoid process was of unusual interest. It occurred in a girl aged 18 years and followed a fall to the floor while the girl was dancing with her sister. Immediate paralysis of the extremities occurred and death followed in a short time. It was learned that seven years previously, following a fall, both upper extremities had been paralyzed. Complete recovery occurred. Examination revealed that the fracture that caused death occurred in the line of a healed fracture that must have been sustained at the time of the previous injury. The fracture occurred, as do most fractures of the odontoid process, at the line of fusion of the process, which in its embryologic development represents the body of the first vertebra, with the body of the second vertebra. The mechanism of the injury to the cord resulting from such fractures is discussed, and the cord changes due to the previous fracture are described. The author applies the name epistropheus to the second cervical vertebra. Some readers may find considerable interest in the half page historical footnote that describes the confusion in the older anatomic literature due to the fact that the name epistropheus was first applied to the atlas and later, by Heister, to the axis.

O. T. SCHULTZ.

CRIMINAL ABORTION BY INTRA-UTERINE INJECTION OF FLUIDS. E. FRITZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:165, 1930.

In one case, a powdered soap solution was used, which not only caused local escharotic changes of the vagina and uterus, but penetrated into the general circulation, producing grossly visible alterations of the muscle of the heart, the liver and the kidneys. The hemolytic action of the soap is due to its fatty acids. In the second case, an alum solution was injected into the uterus. Embolic air was found in the small arterial branches throughout the body, while the right ventricle of the heart was not distended and did not contain air, but fluid blood. These peculiar results are explained by the presence of a large, open foramen ovale through which the air escaped into the left ventricle and the general circulation. Alum solution was also found in the right ovarian vein.

E. L. MILOSLAVICH.

AIR IN THE BLOOD FOLLOWING CONTUSION OF THE CHEST. O. SCHMIDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:174, 1930.

Severe contusions to the thorax often lead to an interstitial emphysema of the lungs, with hemorrhages in the pulmonary tissue, indicating a great increase of air pressure within the lungs, which also may force the air into the blood. Of forty-five cases of contusion of the chest, the presence of air in the heart or in the blood vessels was proved in twenty-two instances. Air may be found in either ventricle of the heart, because the anterior bronchial veins and the pulmonary veins empty into the left side of the heart while the posterior bronchial veins and the intercostal veins lead into the right side. Often, the left ventricle does not show air, because the air rapidly passes into the peripheral circulation. Air in the smaller blood vessels is best observed in the coronary vessels (rosary-like arrangement of minute air bubbles), where it was seen in eight instances. The minute vessels of the plexus chorioideus may also contain air. A simple apparatus for collecting free oxygen from the heart is described, with the aid of which the oxygen can be (alkaline pyrogallol) quantitatively determined. It seems that the author is not familiar with the important work of LeCount on this subject.

E. L. MILOSLAVICH.

CALCIFICATIONS OF THE BRAIN FOLLOWING GUNSHOT WOUND OF THE HEAD. RAESTRUP, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:181, 1930.

At the autopsy of a man, aged 42, who died shortly after an accident, the brain contained six large areas of calcification, ranging in size from that of a hazelnut to that of a plum. These changes are explained as the result of a gunshot wound of the head which the man accidentally sustained at the age of 10 years (calcification of old encephalomalacic or hemorrhagic areas). During life no physical or psychic disturbances were observed.

E. L. MILOSLAVICH.

THE FORENSIC SIGNIFICANCE OF GASEOUS DECOMPOSITION AFTER ABORTION. P. FRAENCKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:216, 1930.

A case is described of rapid intra-uterine destruction of the soft tissues of the fetus by gas-forming organisms. The fetus was at about the sixth month, and the soft parts were destroyed quite completely in from twenty-seven to thirty-six hours. A large postmortem rupture of the uterus also developed within the same time. The importance of distinguishing between ordinary cadaveric decomposition and the effects of the gas bacilli is emphasized. Rapid decomposition of the bodies of young women with gas formation should arouse the suspicion of intra-uterine gas sepsis, an almost certain indication of abortifacient procedures. After death it may be difficult, if not impossible, to distinguish between a vital gas sepsis and postmortem invasion of gas bacilli. Further efforts should be made to determine whether changes due to the infection can be recognized in spite of the decomposition.

THE CONDITION OF HUMAN BODIES RECOVERED FROM PEAT BOGS. M. GABRIEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:226, 1930.

Acids and other substances in peat bogs have a peculiar preservative effect on the human body. The recorded observations on human bodies recovered from peat bogs in northern Germany are reviewed by Gabriel at the same time as she describes a body recently found in a bog in the southern part of the country. The most noteworthy effects are a sort of tanning of the skin and decalcification of the bones. Usually the bodies are greatly compressed; the skin is deep brown; the bones are brown, elastic and easily cut; the cartilage, teeth and nails are preserved and the soft tissues and organs are not recognizable. Woolen clothes remain practically unchanged and afford a means of forming some idea of how long since a given body came to rest in the bog.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 13, 1930

JOSEPH A. CAPPS, *President, in the Chair*

THE PATHOGENESIS OF CARDIAC PAIN. JOSEPH A. CAPPS.

I have chosen this subject for consideration because it is of vital interest to both pathologists and internists. Cardiac pain, with its characteristic quality, its location over the region of the heart and its extension to distant parts, is familiar to every physician. But the origin of this pain and the factors initiating its mechanism have taxed the ingenuity of the pathologists and physiologists alike.

The approach to this problem may be made conveniently by discussing the first pathologic evidence; second, the clinical manifestations, and finally, the physiologic theories that will most adequately explain the facts observed by the pathologist and the clinician.

Pathologic Anatomy.—The necropsy observations on persons who have suffered from cardiac pain, whether they died of heart disease or of some other disease, bring the lesions of certain structures into focus as probably related to the patient's complaint, viz., lesions in the aorta especially in the vicinity of the aortic valve, in the arteries of the heart and in the myocardium.

Frequently degenerative changes are present about the aortic valve with thickening or atheromatous patches, and these changes may so impinge on the orifice of the coronary arteries as to impede the filling of these vessels. In many cases sclerosis of the coronary arteries is discovered, sometimes diffuse, but often localized in portions of the main arteries or in the small branches. These localized areas of degeneration may be fibrous or they may be calcifications that narrow the lumen. In a smaller group actual occlusion of the coronary arteries occurs with infarction of the muscles of the heart. The infarcted region, if small, may heal and is recognized by fibrous changes in the wall, or, if larger, may lead to aneurysmal thinning or even rupture of the myocardium. Although narrowing of the arteries is the usual condition, there are instances of dilated vessels, at times localized and leading to aneurysm of the artery itself, which may perforate into the pericardial sac.

From the pathologic point of view, then, it seems that degenerative changes in the aorta near the ring and in the coronary arteries, with resulting interference with the blood supply of the muscle of the heart, offer a basis for the clinical symptoms of pain.

Unfortunately for this hypothesis a considerable number of necropsies exhibit similar damage to the aorta and coronary arteries even with extensive infarcts, without a history of pain. Furthermore, a smaller group of patients who have experienced definite severe cardiac pain may have little or no vascular damage post mortem.

The pathologist, therefore, must look on these lesions as significant in the interpretation of pain, but not as a full and final explanation.

Clinical Observations.—It is noteworthy that in most forms of so-called "heart disease" pain is absent. Valvular endocarditis, arrhythmias, decompensation with dilatation and hypertrophy are usually associated with dyspnea, but not with pain. The reaction of pain seems quite uniformly to be associated with disturbances of the vascular supply to the muscle of the heart. Thus one sees cardiac pain in young, healthy persons, during strenouous exercise. In older persons with signs of heart trouble, pain is induced by effort or excitement or by excessive smoking, i. e., factors which greatly increase the normal demand of the muscles of the heart

for blood. It is inferred that pain occurs only when this urgent demand cannot be met by a corresponding increase in the flow of blood to the tissues of the heart. The second wind of the athlete and the dilating effect of nitrite in the cardiopath are interpreted as a fulfilment of this demand by the delivery of a greater volume of blood.

Hence it is that all the theories of cardiac pain implicate the vascular system of the heart. The principal theories of the origin of cardiac pain are: Nothnagel's (*Ztschr. f. klin. med.* **19**:209, 1891) conception of pain arising in the arteries themselves; Allbutt's (Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915) idea of the aortic ring as the region which provokes pain, the condition of tension playing the important rôle, and Mackenzie's (Angina Pectoris, London, Oxford University Press, 1923) hypothesis of the muscles of the heart as the starting point of pain. He believes that the contraction of an anemic muscle is sufficient to explain the pain symptom. Most modern writers subscribe to this belief, although the word anoxemia is preferred to anemia.

Without further discussion at the moment, it may be said that the belief in the coronary arteries themselves as the actual seat of pain has been losing ground.

The aortic hypothesis predicates a rise in blood pressure with stretching of the diseased wall of the aorta. Death may ensue from vagal stimulation. But aortic disease is not always present, and there is reason to think that death occurs in angina pectoris from ventricular fibrillation, rather than from vagal standstill.

Keefer and Resnik (*Arch. Int. Med.* **41**:769, 1928) consider that angina pectoris has but one cause — "anoxemia of the myocardium" — which they think is the one constant in the varying conditions associated with the disease, such as coronary narrowing, aortic regurgitation and pernicious anemia.

Physiologic Considerations.—The heart is supplied by sympathetic and vagus nerve fibers, the former certainly being capable through afferent impulses of provoking pain in the spinal nerves, the latter probably so. It may well be that the heart gives rise also to an intrinsic, or in the sense of Ross, a protopathic, pain localized in the region of the heart (substernal). This is the most constant of all cardiac pains. Similarly, the stomach has its protopathic epigastric pain, as well as its pains referred to distant parts.

Now, like all the hollow viscera, the muscle of the heart is insensitive to pain from ordinary stimuli, such as scratching, cutting and cauterizing. I have found this to be true of the epicardium, and Sutton and King (*Proc. Soc. Exper. Biol. & Med.* **25**:842, 1929) could tear the myocardium and pericardium of dogs without causing pain. But like other hollow viscera, the heart may respond with pain to the adequate stimulus. Spasmodic contraction and at times distention are the adequate stimuli in other hollow organs, e. g., pyloric spasm, biliary colic, etc.

Can cardiac pain be explained on the theory of distention or cramping of the muscles? Swelling of the muscles might set up pain, but localized edema or engorgement does not result from sudden occlusion of an artery; the first effect is anemia. Acute dilatation of the chambers of the heart, as is known from fluoroscopic observation, does not take place in attacks of angina.

One can be equally sure that during an attack of cardiac pain the heart as a whole does not go into spasmodic contraction. Careful studies of the beats of the heart by electrocardiographic tracings and by direct roentgen observations show no such tendency. Sudden death comes not by spasm but by ventricular fibrillation.

Spasm or cramping of the anoxemic portion of the muscle of the heart, i. e., localized spasms, is not so readily excluded. However, it may be stated that no direct evidence supporting this view has been offered. A pain analogous to cardiac pain, with anoxemia of the muscles, can be seen in the intermittent claudication of the legs, in which a similar background of arteriosclerosis or arterial spasm is present. This pain is induced by effort just as is that in the heart. The pain

is apparently not accompanied by muscular cramp, or at least there is no obvious knotting of the muscles. A localized cramp in the muscle of the heart would certainly disturb the rhythm profoundly. As stated, a patient may go through a severe attack of angina with no marked alteration of the electrocardiogram.

One is justified, I believe, in excluding acute distention or spasmodic contraction of the muscle of the heart, either as a whole or localized, as determining factors in the production of cardiac pain.

This brings me to the only tenable hypothesis based on the myogenic origin of cardiac pain, viz., that the pain is provoked in the anoxemic muscle during contracture. In the heart the contractures are rhythmic and continuous. If the occlusion of a coronary artery is complete, as in thrombosis, the pain is continuously excited. If the occlusion is partial, pain comes on only when exercise renders the muscle highly anoxemic.

However, this theory is not altogether satisfactory. Why is it that in a considerable group of cases of partial coronary occlusion with dyspnea, cyanosis and other signs of anoxemia there is no pain? Why is it that even extensive infarcts take place with aneurysm and rupture of the wall without pain? In these cases there are certainly the two factors of muscular contracture and anoxemia. Is it possible that certain parts of the wall of the heart are silent areas with reference to pain response? Why is it that the onset of fibrillation or decompensation in cases of angina tends to lessen or eliminate the pain? Do these complications, which bring further damage to the heart, lessen the anoxemia? One would infer that anoxemia would be increased.

It seems that Nothnagel's idea of pain originating in the arteries themselves during constriction deserves further investigation. Arteries are hollow organs and may react to pain as other hollow organs. A stone in the ureter excites pain not from distention, but only during spasmodic contraction of the muscular tube in its effort to propel the stone onward. Between attacks of colic, though the stone still distends the duct, the pain ceases. Likewise, there are the bearing down pains of the uterus with severe contraction and absence of pains with relaxation, although distention continues.

Attempts have been made to produce anginal pain in animals and to determine the mechanism of pain. Singer *(Wien. Arch. f. inn. Med.* **14**:113, 1927) found that coronary arteries, when stripped of their adventitial covering, were insensitive to clamping, pricking and mechanical and electric stimulation. Ligation of the stripped coronary artery, causing anoxemia, did not produce pain response. The coronary arteries, however, left intact in their adventitial coats, were highly sensitive to mechanical and chemical stimulation.

On the other hand, Pearcy, Priest and Allen (*Tr. A. Am. Physicians* **42**:243, 1927) reported signs of severe pain in forty of fifty experimental dogs after occlusion of the coronary arteries by clamping or ligature.

Sutton and King demonstrated that ligature of the coronaries usually gave evidence of pain, while tying of muscle and pericardium only did not induce pain. Their experiments might give support to the vascular as opposed to the myogenic origin of the pain.

Further study should be pursued to determine these points. Is arterial constriction or spasm a constant accompaniment of cardiac pain? Does the absence of pain after ligature of the stripped arteries signify the absence of coronary spasm? Is there severe arterial spasm with most cases of infarct with correspondingly severe pain, and in other cases of occlusion is there little or no spasm and consequently little or no pain? Does the subsidence of pain a few days after infarct indicate simply the disappearance of vasoconstriction? These questions, I believe, can be answered by well directed experiments.

ADDISON'S DISEASE WITH SELECTIVE DESTRUCTION OF THE SUPRARENAL CORTEX ("SUPRARENAL CORTEX ATROPHY"). H. GIDEON WELLS.

This article was published in full in the October, 1930, issue of the ARCHIVES, page 499.

THE PATHOGENESIS OF MALIGNANT NEPHROSCLEROSIS. PHILLIP SHAPIRO.

A study is reported of the material on nephrosclerosis available from 1,000 consecutive autopsies at the Cook County Hospital on patients over 20 years of age. There were 171 cases of nephrosclerosis, 36 with uremia, 135 without. An injection method with india ink was applied to check the observations of direct examination. It was found that the histologic changes of malignant nephrosclerosis were intimately and proportionately associated not with ischemia, but with hyperemia, which was direct and not retrograde. These observations were analyzed on the basis of Gustav-Richer's views on the hemodynamic changes of sclerosis. Malignant nephrosclerosis, in pathogenesis, seems to be only an accelerated form of benign nephrosclerosis, and both are based not on ischemia as such, but on a retardation hyperemia.

SPONTANEOUS BILATERAL DECAPSULATION OF THE KIDNEYS. WILLIAM M. MCGRATH and CARL W. APFELBACH.

Two kidneys with a watery fluid in their capsules were presented. The names commonly given to this condition are perirenal hydronephrosis, perirenal hygroma and renis hydrocele. The cases so far reported in the literature of accumulations of fluid in the capsules of the kidneys are explained by the authors as collections of lymph from blockage of the lymph channels and as exudates from inflammation of the renal capsule, from hemorrhage and from the extravasation of urine. The gross and histologic evidence in these two specimens points as much to extravasation of urine within the capsules of the kidneys as it does to blockage of the lymph channels. The alterations in the capsule are those of encapsulation, and inflammation seems to be a remote etiologic explanation.

Regular Monthly Meeting, Nov. 10, 1930

JOSEPH A. CAPPS, M.D., *President, in the Chair*

SILVER IMPREGNATION OF GLIOMAS WITH DAVENPORT'S METHOD. ARTHUR WEIL.

The method, which had been published previously, was described (Arthur Weil and Harold A. Davenport: Eine Methode zur Silberimprägnierung von Gliomen, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **126**:796, 1930). Lantern slides were projected demonstrating the resemblance of different cellular elements of an embryonic spinal cord of a rat embryo nineteen days' of age with the tumor cells of different gliomas. The classification of Bailey and Cushing was discussed in connection with this comparative material.

EXPERIMENTAL GRANULOMA INDUCED BY INFECTION WITH B. FUSIFORMIS. JACOB KLEIN.

B. fusiformis is a frequent and important inhabitant of the mouth and is associated with Vincent's spirillum in stained preparations from Vincent's gingivitis, balanitis, abscess of the lungs and infected sinuses. The rôle of fusiform bacilli as pathogenes is uncertain. Thus, Varney isolated eighteen strains of *B. fusiformis*, and found that they were not pathogenic for dogs and rats. Larson and Barron noted that the successful inoculations have been made almost invariably with material taken directly from lesions of patients and not with cultures.

B. fusiformis is a pleomorphic, granular, Gram-negative anaerobe. The strain used in these studies was isolated from a patient suffering from Vincent's gingivitis, and was grown anaerobically in a Varney jar on Rosenow's brain broth medium. There is a white flocculent growth in the brain broth medium, and a white pellicle forms on the surface. Colonies on serum agar plates are from 1 to 2 mm. in

diameter and white or yellowish-white with fringed or saw-tooth contour. After repeated subcultivation, it was possible to obtain a growth in the brain broth medium under ordinary conditions without the use of the Varney jar. During these studies there was no indication that the spirillum develops from the bacillus, as has been claimed by Tunnicliff.

Dogs into which *B. fusiformis* is injected or which are fed with the organism in pure culture become ill, and extremely emaciated and die within two weeks or four months, depending on the mode of infection. The changes in tissue consist of a reticulo-endothelial hyperplasia of the lymph nodes, lymphocytic infiltration and necrosis of the liver, subacute interstitial inflammation of the lungs associated with foci of necrosis, ulceration of the mouth and, in several instances, necrosis and fibrous changes of the mesenteric lymph nodes.

Hitherto *B. fusiformis* has been considered innocuous in animals. On the basis of the experiments I believe that *B. fusiformis* causes a subacute infection and death in dogs. The fusiform bacillus in pure culture may cause a bleeding gingivitis in man, as was demonstrated by an accidental laboratory infection sustained by the author.

There is clinical evidence that indicates that a Vincent's stomatitis may be associated with agranulocytosis and leukemic reactions, although the exact nature of the relationship is not clear. In this preliminary report it was desired to indicate an interesting field for study. Detailed hematologic data will be presented later.

DISCUSSION

J. A. CAPPS: There seems to be a relation between agranulocytic angina and infections with *Bacillus fusiformis*. Do these organisms have any action on the bone marrow, especially do they cause inhibition in the production of polymorphonuclear leukocytes?

I. PILOT: Small doses of *B. fusiformis* are without effect on animals, but when mixed with *Streptococcus* a putrid lesion results.

R. H. JAFFE: It is important to demonstrate the fusiform bacilli by culture or stains in the lesions.

J. KLEIN: I was unable to demonstrate the organisms in the lesions. With other organisms *B. fusiformis* has been recovered from the blood.

DISSECTING ANEURYSM OF THE AORTA. EVAN M. BARTON.

The clinical diagnosis of dissecting aneurysm of the aorta is infrequently made in the presence of this disease. The symptoms often simulate those of more frequent diseases, and in other instances the patients are not under clinical observation long enough to furnish adequate data on which a clinical diagnosis may be made.

W. B., aged 54, was a business man, and had been under the observation of Dr. E. E. Irons for nine years. During the last four years, a progressively increasing essential arterial hypertension had developed.

Seventeen days before death, severe pain occurred in the abdomen above the umbilicus. The pain was intermittent and radiated to the shoulders and dorsal wall of the trunk. Morphine partially relieved this symptom. The systolic blood pressure was 270 mm. of mercury, the diastolic 170. The pulse rate was 68 per minute. The systolic thrust was pronounced. Restlessness, sweating and pallor were accentuated during the painful periods. There was no rigidity of the abdominal wall, but soreness and tenderness were present in the epigastrium.

Within twenty-four hours after the onset, fluid began to collect in the left pleural cavity. For six days the patient seemed to be improving. A roentgenogram taken on the seventh day demonstrated a widened and tortuous aortic arch and a widened descending portion of the aorta.

The abdominal pain persisted so intensely that morphine was required at increasing intervals, day and night. During one day, the patient complained of

severe precordial pain and oppression in the chest; on another, the complaint was a feeling of oppression around the heart; on still another occasion, the pain radiated to the left lateral wall of the chest.

Mental confusion developed during the last few days and increased until the last day, when he became irrational and had a generalized convulsion. The systolic blood pressure after the convulsion was 120. Seven hours after the convulsion, while carrying on a conversation with one of the physicians, the patient suddenly collapsed and died in a few minutes.

There was no history of syphilis, and a Wassermann test on blood serum in 1926 gave negative results. The provisional clinical diagnosis was dissecting aneurysm of the aorta.

The anatomic diagnosis was: dissecting aneurysm of the thoracic and abdominal portions of the aorta; extensive hemorrhage into the peri-aortic tissues, mediastinum, right and left pleural cavities, root of the neck and right perirenal tissues; marked sclerosis of the aorta; syphilitic (?) aortitis; marked hypertrophy of the wall of the left cardiac ventricle; general anemia.

The dissection of the wall of the aorta by blood had begun at a tear of the intima along the inferior margin of a calcified plaque, 1.5 cm. in diameter at the obliterated mouth of the ductus botalli. The dissection continued downward in the anterior and right and left portions of the wall of the aorta to the level of the renal arteries; only a strip averaging about 1 cm. in diameter along the right half of the dorsal wall of the aorta escaped dissection. At the upper end of the dissected portion, there was a rupture of the muscular and adventitial coats that allowed the blood to escape into the adipose tissue which surrounded the aorta. From here blood dissected its way into the mediastinum, the root of the neck and the fatty capsule of the right kidney.

In the left pleural cavity, there was about 500 cc. of bloody, watery fluid. The blood had escaped from the mediastinum into the pleural cavity through an opening, which was sealed over by fibrin. In the right pleural cavity there were 2,200 Gm. of clotted and fluid blood that had escaped through a tear in the parietal pleura a few centimeters inferior to the hilus. No free blood was found under the parietal pleura that covered the ribs, and only the left intercostal arteries were directly in the pathway of the dissecting aneurysm.

In microscopic sections of the arch and thoracic portion of the aorta, there were vascular scars in the media, atrophy of the media, and round cell infiltration about these new blood vessels and also about the vasa vasorum of the adventitia.

Summary.—Death resulted from acute anemia due to rupture of the dissecting aneurysm into the right pleural cavity. The most marked alterations of the aorta were those of arteriosclerosis. The dissection of the wall of the aorta began at the inferior margin of a large, elevated, calcified plaque at the site of the obliterated ductus botalli. The changes in this region suggested that the lining was torn, because in an aorta stressed by a blood pressure that averaged 250 mm. of mercury, the large plaque was forced over the more elastic wall immediately distal to it, and at this junction unusual strain occurred.

In the root of the aorta there were histologic changes like those commonly found in syphilitic aortitis. Nowhere else in the body were there gross alterations characteristic of syphilis.

The clinical diagnosis was based: (1) on the pain, which at times resembled the pain associated with thrombosis of the coronary arteries; (2) on the persistence of a high blood pressure; (3) on the absence of an acute abdominal disease, and (4) on the appearance of fluid in the left pleural cavity.

DISCUSSION

J. A. CAPPS: Were roentgen examinations made, and was the patient under treatment for syphilis?

PAUL CANNON: Was syphilis a factor in the lesion?

E. F. HIRSCH: What is the probable duration of the lesion?

E. M. BARTON: The roentgen examination demonstrated a widened and tortuous arch and main portion of the aorta. Syphilis is not the cause of the lesion. The symptoms began seventeen days before death, and probably the lesion did not occur at once.

LEIOMYOSARCOMA OF THE PLEURA. LLOYD CATRON.

In the body of a white woman, aged 83, who had died from severe coronary sclerosis, a tumor mass that measured 22 by 18 by 8 cm. was found incidentally at autopsy, in the left side of the chest cavity. The left lung was markedly compressed. The tumor, well encapsulated by the pleura, was rounded, firm, smooth and gray white, with small hemorrhages on the surface. On section, the mass was seen to be composed of three roughly spherical nodes, the largest of which was 15 by 9 by 7 cm., separated by smaller nodules. The superior node was composed of interwoven red-brown and gray tissue. Elsewhere there were present yellow and soft small areas, and inferiorly there was an irregularly shaped cavity crossed by trabeculae of yellow-gray tissue. There were no metastases. Microscopically, the tumor consisted of two distinct types of tissue forming an irregular network. In one type the cell contained a large ovoid or fusiform, centrally placed nucleus with a fine chromatin net and a distinct nuclear membrane. There were few mitotic figures. The cytoplasm, which stained yellow with van Gieson's stain and red with Mallory's aniline blue, was chiefly fusiform, extending from the nuclear poles as homogeneous bands; in some regions, however, fine cytoplasmic processes extended from the nuclear periphery. The other tissue was a fibrillar connective tissue with long, flattened nuclei between collagen bands. In the cellular portions the connective tissue formed only a scanty stroma composed of fine fibrils. In the capsular pleura, which was from 1 to 3 mm. in diameter, there were distinct bundles of smooth muscle fibers which apparently passed rather abruptly into the large cells of the tumor. Within the growth, disseminated regions of necrosis were found in parts that apparently lacked an adequate supply of blood, and retrogressive changes were present about blood vessels that contained mixed thrombi. Elastic fibers were present only in the thin walls of numerous small blood vessels. The heterotypic morphology of the tumor, the marked variation in size and shape of the tumor cells and the extreme anaplasia of their nuclei led to the diagnosis of a leiomyosarcoma. No report of a smooth muscle tumor originating in the pleura was found in the literature. This pleural sarcoma was of the voluminous type without metastases, several of which have been reported.

DISCUSSION

I. PILOT: The huge size of fibrosarcomas of the lungs and the absence of metastases are noteworthy.

E. R. LONG: What was the origin of this growth?

R. H. JAFFE: The growth probably originated in the smooth muscle of the pleura.

P. DELANEY: With such fully differentiated tissues, is this growth malignant?

R. H. JAFFE: Mitosis and other cellular characteristics favor the conclusion that this is a malignant growth.

Book Reviews

A System of Bacteriology in Relation to Medicine. Medical Research Council. Volumes 1 to 5. Cloth. Price, per volume, 1 pound, 1 shilling, net. London: His Majesty's Stationery Office, 1930. (May be obtained from the British Library of Information, 551 Fifth Avenue, New York.)

This work is published by the Medical Research Council as a "comprehensive but not encyclopaedic" survey of the present knowledge of bacteria and other microbes in their relation to medicine. Each author deals with subjects in which he has a special interest — it is a cooperative work by specialists. The attempt is made to discuss matters that seem "to rest on truth" or are of active concern because they bear on modern practices. Even with the limitations thus imposed the complete work will consist of nine volumes and will be the most comprehensive publication of its kind in the English language up to the present. It is the product of a posse of writers — nearly 100 British bacteriologists participtate — and consequently it becomes impracticable to estimate the merits of each writer. The remarks that follow are based mainly on an examination of the first five volumes. It is a pleasure to commend the type, the size and format and the exceptional handiness of the volumes. And the price is reasonable. Volume 1 deals with general bacteriology: morphology, physics of bacterial cell, growth and reproduction, nomenclature and variation. Volume 6 will deal with the distribution and spread of bacteria, virulence and immunity. William Bulloch contributes to volume 1 a valuable summary of the history of bacteriology. An innovation is the insertion in the chapters on important bacteria of a brief historical account by the same author. The following comment from the chapter on nomenclature by F. W. Andrewes will meet with a sympathetic response from many: "One of its [American classification] chief features lies in the creation of a number of new genera to indicate the natural groups into which the rod-shaped bacteria fall, and new generic names have been formed, on both sides of the Atlantic, from the names of prominent workers in the science. Sometimes the result has been not inartistic; such names as *Salmonella, Brucella* and *Pasteurella* are pleasing to the ear and pay a well-deserved compliment to distinguished men. Nevertheless, marriage between Northern names and Latin terminations is seldom a happy practice, and we might well have been spared such barbarisms as *'Escherichia'* and *'Mcintoshiella.'*"

Arkwright's chapter on variation merits special commendation as a lucid, sane and helpful discussion of an intricate subject. He comments instructively on variability in streptococci as follows: "It seems probable that some of the variability described has been due to impurity of the original culture, an accident which is especially likely to occur in dealing with minute colonies of the streptococcus, a class of organism comprising many species and races which occur together and are very similar in morphology."

Volumes 2, 4 and 5 are concerned with pathogenic bacteria; volume 3, with economic bacteriology, plague, gas gangrene, botulismus, tetanus and bacterial food poisoning. The single volumes have no indexes; the general subject index will appear in volume 9. The titles on the backs of the volumes are helpful, of course, but in some cases the titles do not indicate the contents fully; for instance, it would be impossible to locate the chapter on tularemia from these titles. All references to articles are given without titles; as a rule, references are placed at the end of the chapter, and as most of them are without titles they will have little value by themselves without reference to the text. Exceptionally, as in the chapter on tuberculosis, the appropriate references are placed at the end of sections, which has the advantage of an analytic grouping. The references at the end of the chapter on streptococci occupy no less than fifteen pages, and in such cases it

would be more helpful if they were listed appropriately with the main sections, which frequently have different authors, as the major chapters commonly are made up of articles by two or more authors. Of the first five volumes only the first and third (soil bacteria) contain illustrations, all in black and white. Comment on the lack of illustrations is hardly worth while, as it is obvious that more illustrations would have increased the cost unduly in view of the excellent illustrations of bacteria in readily available publications. Generally the articles reflect satisfactorily the state and trend of the knowledge of the subjects considered. Occasionally recent developments, e. g., in toxin production by certain streptococci, in brucellosis and in the cutaneous reactions to gonococci and their products, do not seem to have caught the full attention of the writers. On the other hand, too much stress may be placed on matters of little importance. To devote nine pages to sanocrysin is hardly worth while—it is not a live subject and the claims first urged so recklessly in its favor did not "rest on truth." In some articles there are too many bald facts cataloged, sometimes in roundabout phrases. But taken as a whole the first five volumes of the system present a well considered and helpful summary of the contemporary knowledge in the fields of bacteriology with which they deal.

NAISSANCE, VIE ET MORT DES MALADIES INFECTIEUSES. By CHARLES NICOLLE, Director of the Pasteur Institute of Tunis, and winner of the Nobel Prize in Medicine for 1928. Paper. Price, 15 francs. Pp. 219. One of the Nouvelle Collection Scientifique, Director, Émile Borel. Paris: Félix Alcan.

This volume by Charles Nicolle, whose work on typhus fever resulted in the award to him of the Nobel prize in medicine, 1928, is, in the words of the author, addressed to no particular category of readers. It is essentially a readable expression of the philosophy of one who has observed infectious diseases from all angles. No particular knowledge of infections is assumed, and the numerous examples used as illustrations of various points contain much that is not intended to inform the medical reader. Nevertheless, the author's intimate knowledge, obtained at first hand, regarding the matters discussed is such that the interest of any reader is well sustained.

The title suggests logically the origin, existence and elimination of infectious diseases per se. The contents treat serially of the existence, origin and elimination, arguing from the known to the unknown and philosophical, or, at times, as the author admits, the speculative. At no time, however, is one entitled to criticize the author's statements as being fantastic. As an experienced investigator, he is ever anxious to support his statements and to admit the weaknesses in his theories. And his long struggle with infections has resulted in a ready recognition of the inadequacy of human effort. In discussing the purely natural phenomena, however, he treats them scientifically, stressing the point that natural methods are purely random, based principally on chance; and thus the human efforts, though they be weak and impotent for the most part, are valuable in that they are directed. Dr. Nicolle has not ceased fighting, and he would not discourage his readers. His method is not didactic; "ce livre est un *essai*" are his first words.

It is difficult even to outline the general subject matter of the volume. A long-range perspective toward all infections is attempted. The various phases of the evolution of such diseases are considered in nature, as modified by human effort, and as modified by changes in the mode of existence of man and animal hosts. It is argued that certain facts have been definitely revealed in modern studies. Based on these facts, historical evidence may in many instances be properly interpreted, thus enabling one to picture the trend of infections over long periods. "An infectious disease changes, evolves unceasingly." The spread of diseases, as, for example, the importation of syphilis from Mexico, where Bernal Diaz de Castillo recorded the disease, into Europe (sic), illustrated one point of attack. Historical study may be complemented by experimental investigation. Thus the matter of virulence, of adaptation of pathogenic organisms to special organs, the

variation in the host and the survival of organisms during latent periods are all considered. The *"infections inapparentes,"* or invisible types of true specific infection noted experimentally in typhus fever by Nicolle and considered by him to be perhaps relatively common in other diseases, are discussed as indicating evolutionary changes and as reservoirs in the spread of infections. Finally, a venture as to the future trends in infections is offered, although it is unfair to the author to convey the impression that he essays the rôle of prophet. He deals primarily with existing and modern data; one infectious disease may have disappeared years ago, others may be developing. It appears logical to the author to expect a greater diversity of infections, yet a lower mortality — increasing evolutionary changes in the agent of infection and in its host and environment with more complex civilization, and decreasing mortality with better knowledge of the manner of combating diseases and greater dissemination of gradually acquired immunity. The volume ends: "We have confidence in those who follow us. Peaceful and better, they will know better how to defend themselves, to protect their kind and animals useful in their lives against the dantesque but unintelligent, undisciplined rabble of infectious diseases."

ALLERGIE DES LEBENSALTERS: DIE BÖSARTIGEN GESCHWÜLSTE. By DR. CLEMENS PIRQUET, o. ö. Professor an der Universität Wien. Paper. Price, 23 marks. Pp. 170, with 143 illustrations. Leipzig: Georg Thieme, 1930.

This monograph presents a detailed analysis of the age and sex incidence of 697,515 cases of malignant tumors, contained in the report of the Registrar General of England and Wales, between the years 1911 and 1926. This material is probably the largest that has ever been subjected to such a statistical analysis. The contents reveal many facts already well known regarding the age incidence of different forms of cancer and support the conclusions reached by previous authors dealing with a smaller material.

The author's final graph (page 120) shows the existence of several notable features in age incidence. The tumors of the kidney and suprarenal gland occur mainly in the first fifteen years of life. These must be mainly of congenital type. The second group, tumors of the bone, finds its peak about the eighth or tenth year. The third group, testicular tumors, is most frequent in the thirty-third year. Tumors of the brain are most frequent in the forty-sixth year. Other varieties reach their peaks at later periods, from 55 to 70. Tumors of the skin are last on the list, with a peak at 76.

Lymphogranuloma gives a graph which varies notably from the tumor type, this disease occurring rather uniformly in many decades and without any definite peak.

The work contains many separate analyses of the different forms of tumors and extensive tables showing the numbers of cases of each type at different ages.

While the size of the material handled renders this study one of much importance, it may be questioned as to what extent the diagnoses on the death certificates were accurate. Only a small proportion were proved by autopsies. The material naturally does not permit of a separation of the different types of cancer occurring in the same organ, and this deficiency must apply to most statistical material now available. Many will find it a serious limitation to the value of statistical studies of this type.

The author has taken a strictly mathematical view of his task and has limited himself, perhaps unnecessarily, in the interpretation of the clinical and pathologic significance of the facts which he demonstrates.

The figures are not corrected with reference to the total population living at the different periods of life, so that the reader must be warned that the graphs give no indication of the liability to cancer at different age periods.

As a volume of reference, the monograph will be of definite value. It possesses a peculiar interest as a posthumous publication from the study room of a lamented and highly esteemed worker.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D., Professor of Pathology, University of Minnesota, Minneapolis. Contributors: E. T. Bell, M.D., Professor of Pathology; B. J. Clawson, M.D., Professor of Pathology; Hal Downey, M.D., Professor of Hematology; J. S. McCartney, M.D., Assistant Professor of Pathology; J. C. McKinley, M.D., Professor of Neuropathology and Neurology, and C. J. Watson, M.D., Instructor in Pathology, University of Minnesota, Minneapolis. Cloth. Price, $8, net. Pp. 627, with 316 engravings, of which 313 are original, and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

This is a cooperative attempt by several pathologists in the same medical school "to present the essential facts of pathology to medical students." A special effort is made "to bring the structural changes in disease [pathologic anatomy] into close relation with the problems of clinical teaching." The first twelve chapters, all by the editor, except the chapter on the mycoses by J. S. McCartney, deal with general pathologic processes and cover about 272 pages. The topics ordinarily included under general pathology are discussed clearly and succinctly, mainly from the morphologic standpoint. Hodgkin's disease is included under tumors of the blood-forming tissues and treated as if there were no question about its nature. E. T. Bell also wrote the chapters on the genito-urinary systems, the blood vessels, certain acute infectious diseases, the thymus and lymph nodes, the respiratory system, the digestive system, the ductless glands and certain diseases caused by animal parasites. The use of the term Malta fever in place of undulant fever or, better perhaps, brucellosis or brucelliasis is unfortunate. The chapter on the heart is by B. J. Clawson; that on the spleen by C. J. Watson; that on the liver and gallbladder by J. S. McCartney; that on neuropathology by J. C. McKinley, and that on diseases of the blood by Hal Downey. The presentation is clear, orderly and competent. The illustrations, all original, are good and were chosen with discrimination. The references to the literature will help the student. The principles of microbiology and immunology are not considered. Throughout the book, "pathology" is used commonly as synonymous with "pathologic anatomy," and the book is essentially a concise but thoroughly reliable text for medical students on general and special pathologic anatomy.

PHYSIOLOGY AND BIOCHEMISTRY OF BACTERIA. VOLUME II: EFFECTS OF ENVIRONMENT UPON MICROÖRGANISMS. VOLUME III: EFFECTS OF MICROÖRGANISMS UPON ENVIRONMENT. FERMENTATIVE AND OTHER CHANGES PRODUCED. Cloth. Pp. 575. By R. E. BUCHANAN, PH.D., Professor of Bacteriology and Bacteriologist of the Iowa Agricultural Experiment Station, Iowa State College, and ELLIS I. FULMER, PH.D., Professor of Biophysical Chemistry, Department of Chemistry, Iowa State College. Cloth. Price, $7.50 per volume. Pp. 709. Baltimore: Williams & Wilkins Company, 1930.

The jocose remark that scientific men should now proceed to take a vacation of ten years to catch up with science and find out what it is all about has its serious side. The mass of detail that is annually published in practically every field of investigation seems at times likely to overwhelm one. Fortunately there are still workers who are willing and competent to face the task of compiling, editing and sifting, and who can organize and make accessible the results of thousands of detailed pieces of research. Buchanan's successful accomplishments in this field are well known, and the second and third volumes of his monumental work on the physiology and biochemistry of bacteria will be welcomed by all students of microbiology. There is little to criticize in arrangement or choice of material. The style is clear and straightforward. The extensive bibliographies are wonderfully complete. The text is slightly marred by the occasional misprinting of proper names, but in general the proofreading is excellent. Altogether these two volumes will aid the real progress of science.

Books Received

PHYSIOLOGY AND BIOCHEMISTRY OF BACTERIA: II. EFFECTS OF ENVIRONMENT UPON MICRO-ORGANISMS. By R. E. Buchanan, Ph.D., Professor of Bacteriology and Bacteriologist, Iowa Agricultural Experiment Station, Iowa State College, and Ellis I. Fulmer, Ph.D., Professor of Biophysical Chemistry, Department of Chemistry, Iowa State College. Price, cloth, $7.50. Pp. 709. Baltimore: Williams & Wilkins Company, 1930.

PHYSIOLOGY AND BIOCHEMISTRY OF BACTERIA: III. EFFECTS OF MICRO-ORGANISMS UPON ENVIRONMENT: FERMENTATIVE AND OTHER CHANGES PRODUCED. By R. E. Buchanan, Ph.D., Professor of Bacteriology and Bacteriologist, Iowa Agricultural Experiment Station, Iowa State College, and Ellis I. Fulmer, Ph.D., Professor of Biophysical Chemistry, Department of Chemistry, Iowa State College. Price, cloth, $7.50. Pp. 575. Baltimore: Williams & Wilkins Company, 1930.

LABORATORY MEDICINE: A GUIDE FOR STUDENTS AND PRACTITIONERS. By Daniel Nicholson, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba; Assistant in Pathology, Winnipeg General Hospital. Price, cloth, $6.00, net. Pp. 437, with 108 engravings and 1 colored plate. Philadelphia: Lea & Febiger, 1930.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. Bell, M.D., Professor of Pathology, University of Minnesota, Minneapolis. Contributors: E. T. Bell, M.D., Professor of Pathology; B. J. Clawson, M.D., Professor of Pathology; Hal Downey, M.D., Professor of Hematology; J. S. McCartney, M.D., Assistant Professor of Pathology; J. C. McKinley, M.D., Professor of Neuropathology and Neurology; C. J. Watson, M.D., Instructor in Pathology, University of Minnesota, Minneapolis. Price, cloth, $8.00, net. Pp. 627, with 316 engravings, 313 of which are original, and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

LANE LECTURES ON EXPERIMENTAL PHARMACOLOGY AND MEDICINE. By Rudolf Magnus, Late Professor of Pharmacology and Director of the Institute, University of Utrecht, Utrecht, Holland. Price, paper, $1; cloth, $1.50. Pp. 108, with 42 text figures. Stanford University Press, 1930.

THE ANTISCURVY VITAMIN IN APPLES. By Mary F. Bracewell, E. Hoyle and S. S. Zilva. Medical Research Council Special Report series, no. 146. Price, 9 pence, net. Pp. 45. London: His Majesty's Stationery Office, 1930.

THE ELECTROCARDIOGRAM. By W. H. Craib, Medical Research Council Special Report Series, no. 147. Price, 1 shilling, 3 pence, net. Pp. 57. London: His Majesty's Stationery Office, 1930.

MONOGRAPHS ON EXPERIMENTAL BIOLOGY: OXIDATION-REDUCTION POTENIALS. By L. Michaelis, M.D., Member of the Rockefeller Institute for Medical Research. Translated from the German manuscript by Louis B. Flexner, Jacques Loeb Fellow in Medicine, Johns Hopkins Hospital. Price, $3. Pp. 197, with 16 illustrations. Philadelphia: J. B. Lippincott Company, 1930.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE: VII. VIRUS DISEASES, BACTERIOPHAGE. By the Medical Research Council. Price, cloth, 1 pound, 1 shilling, net. London: His Majesty's Stationery Office, 1930. (This may be obtained from the British Library of Information, 551 Fifth Avenue, New York.)

LEGAL MEDICINE AND TOXICOLOGY. By Ralph W. Webster, M.D., Ph.D., Late Clinical Professor of Medicine (Medical Jurisprudence), Rush Medical College, University of Chicago. Price, cloth, $8.50. Pp. 862, with illustrations. Philadelphia: W. B. Saunders Company, 1930.

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